Library

SECOND SERIES VOL. IV, No. 3

BULLETIN

OF

THE NEW YORK

ACADEMY OF MEDICINE

MARCH, 1928

INSTITUTED 1847

PUBLISHED MONTHLY BY
THE NEW YORK ACADEMY OF MEDICINE
Fifth Avenue and 103rd Street
NEW YORK, N. Y.

SECOND SERIES VOL. IV, No. 3

BULLETIN

OF

THE NEW YORK

ACADEMY OF MEDICINE

MARCH, 1928

INSTITUTED 1847

PUBLISHED MONTHLY BY
THE NEW YORK ACADEMY OF MEDICINE
Fifth Avenue and 103rd Street
NEW YORK, N. Y.

Entered as second-class matter, February 3, 1928, at the postoffice at New York, N. Y., under the Act of August 24, 1912.

Subscription $2.00 per year. Single copies, 25 cents.

CONTENTS

PAGE

Papers delivered at stated meetings:

SYMPOSIUM: MALARIA IN SYPHILIS, December 1, 1927:

I. The Place of Malaria in the Treatment of General Paralysis, HENRY A. BUNKER, JR., and GEORGE H. KIRBY 307

II. Clinical Results Following Malarial Therapy in General Paresis, CHARLES W. STONE..... 322

III. Experiences With Malarial Inoculation in Syphilis, JAY F. SCHAMBERG..... 329

A SYMPOSIUM ON THE USE OF ANTIPNEUMOCOCCIC REFINED SERUM IN LOBAR PNEUMONIA, December 15, 1927:

I. The Control, JESSE G. M. BULLOWA..... 339

II. The Relation of Bacteriemia in Lobar Pneumonia to Prognosis and Serum Therapy, MILTON B. ROSENBLUTH..... 343

III. The Method of Administration and the Dosage of Antipneumococcus Serum in Lobar Pneumonia, WILLIAM H. PARK and MISS GEORGIA COOPER

ANNUAL MEETING, January 5, 1928:

On the Significance of Bacterial Allergy in Infectious Diseases, HANS ZINSSER 351

Lobar Pneumonia Considered as a Pneumococcic Massive Atelectasis of the Lung, POL. N. CORYLLOS and GEORGE L. BIRNBAUM 384

Abstracts of papers delivered at section meetings:

Section of Pediatrics, January 12: LEWELLYS F. BARKER February 9: FRITZ B. TALBOT, M. G. PETERMAN..... 400

Section of Surgery, February 3: GEORGE A. WYETH, J. EASTMAN SHEEHAN 411

Section of Neurology and Psychiatry, February 14: SMITH ELY JELLIFFE, JOSEPH J. ELLER, JOHN WYCKOFF, ERNST P. BOAS, JOHN L. KANTOR..... 422

Section of Medicine, February 21: ERNST P. BOAS..... 445

Annual Graduate Fortnight..... 449

Testimonial dinner to Dr. Norris..... 449

Committee on Public Health Relations:

Summary of activities for the month of February..... 452

Proceedings of Academy Meetings, January and February.. 454

Recent accessions to the Library..... 464

Fellows elected February 2, 1928..... 467

Deaths of Fellows..... 467

OFFICERS AND STAFF OF THE ACADEMY

1928

President

SAMUEL W. LAMBERT

Vice-Presidents
CHARLES A. ELSBERG
WILLIAM H. PARK
JOHN E. JENNINGS

Recording Secretary
FENWICK BEEKMAN

Treasurer
SETH M. MILLIKEN

Trustees

JOHN A. HARTWELL
JAMES ALEX. MILLER
GEORGE D. STEWART
ROYAL S. HAYNES
EUGENE H. POOL
BERNARD SACHS
CHARLES L. DANA
SAMUEL A. BROWN
ARTHUR B. DUEL
WALTER L. NILES

Council

The President
The Vice-Presidents
The Trustees
The Treasurer
The Recording Secretary
The Chairmen of
Standing Committees

Director
LINSLY R. WILLIAMS

Assistant Secretary
FREDERICK P. REYNOLDS

Assistant Treasurer
RODERICK V. GRACE

Librarian
ARCHIBALD MALLOCH

Consulting Librarian
FIELDING H. GARRISON

Executive Secretary
Public Health Relations Committee
E. H. L. CORWIN

Legal Counsel
FRANK L. POLK, ESQ.

BULLETIN OF
THE NEW YORK
ACADEMY OF MEDICINE

VOL. IV. MARCH, 1928 No. 3

PAPERS DELIVERED AT STATED MEETINGS

Symposium: Malaria in Syphilis

December 1, 1927

I.

THE PLACE OF MALARIA IN THE TREATMENT OF GENERAL PARALYSIS

A Survey of Four and One-Half Years' Experience in the Use of this Mode of Therapy*

Henry A. Bunker, Jr., and George H. Kirby

The non-specific treatment of neurosyphilis, developed during the past ten years by the Vienna School under the leadership of Wagner-Jauregg, has marked, according to the opinion of many physicians, one of the most notable advances in the field of modern therapeutics. The fact that Wagner-Jauregg was recently awarded the Nobel Prize in Medicine is further evidence of the scientific value set upon his work.

As is well known, the Viennese psychiatrist, after experimenting with various fever-producing vaccines and infections, came to the conclusion that tertian malaria yielded by far the best results in the treatment of the parenchymatous form of neurosyphilis—particularly general paralysis.

Our experience with the malaria treatment began in May, 1923, when we inoculated our first cases of general paralysis. During the past four and one-half years there has been treated at the Psychiatric Institute a total of 251 patients—166 men and 85 women.

*From the New York State Psychiatric Institute, Ward's Island, N. Y.

These have included cases of general paralysis in practically all stages of the disease, the patients with few exceptions having been committed because of their mental disorder to the Manhattan State Hospital. Through the coöperation of the Superintendent of the Hospital, the patients were transferred directly for treatment to the clinical service of the Psychiatric Institute.

The present report will deal only with the male cases, which naturally constitute a major portion of our material. Because the treatment of the female cases was begun at a later period and also because they present certain special features of clinical interest, a report on them will be reserved for a future communication. We further confine this report to a consideration of cases of general paralysis treated almost exclusively by malaria alone; we thus avoid the complicating questions which must arise when various other remedies are used in combination with malaria or supplementary to it.

An inquiry into the place which the malaria treatment occupies or ought to occupy in the therapeutic management of general paralysis might reasonably resolve itself into three questions of immediate practical interest. These three questions are:

(1) What are the clinical results which the malaria treatment is capable of effecting in general paralysis?

(2) What are the disadvantages and drawbacks, and in particular the dangers, inherent in this form of treatment?

(3) What is the duration of the remission of mental symptoms obtained in the cases that respond favorably to malaria treatment—in other words, is the beneficial result a lasting or permanent one?

In attempting to answer the first question, we may cite our experience in the treatment of 156 male patients who completed a course of fever therapy between the dates of June 1, 1923, and August 1, 1927—these 156 patients representing unselected cases in all stages of the disease, with a history of definite mental symptoms antedating admission to the hospital by a period of one month up to three years.

TABLE 1

Clinical Outcome in 156 Male Patients
Treated between June 1, 1923 and August 1, 1927.

		Per Cent.	
Full Remissions	52	33.3	50.6
Well-marked Mental Improvement	26	17.3	
Unimproved, or temporary improvement only	37	23.7	49.4
Died	40	25.7	
(Lost sight of)	1		
Total	156	100.0	

The results so far obtained in this group of patients are presented in Table 1. In our experience, almost the entire degree of mental improvement which can be obtained in the given case is apparent in the vast majority of instances within three months from the completion of the course of fever. It will be noted, therefore, that since even the most recently treated patients in the present group completed their fever therapy four to six months ago, a provisional idea is permissible even in these regarding the character of their response to the treatment.

As is evident from Table 1, one-third of all our patients achieved a complete remission of mental symptoms; they gained good insight, were free from defect symptoms and have been discharged from the hospital and have returned to work. In a few instances, the persistence of residua of a relatively minor character has been sufficient to prevent the patient from resuming his former type of occupation and hence from exhibiting the full degree of his former economic efficiency; but in the great majority of cases these residual symptoms either have been entirely absent or have been so slight or of such a character as not to militate against resumption of the patient's former place in the community.

At this point a word might be said about the occurrence of so-called spontaneous remissions in general paralysis. As is well known, remissions of varying duration occur in cases without the employment of specific or other modes of treatment. The frequency and duration of such remissions has become a matter of considerable interest since the introduction of the newer methods of treatment of general paralysis. The two most careful studies which we have on this subject are those of Tophoff and Raynor. Their results, as shown in Table 2, indicate that spontaneous remissions may be expected to occur in from about 4 to 5 per cent. of hospitalized cases of general paralysis.

TABLE 2

Spontaneous Remissions in General Paralysis

Tophoff (1924)	290 untreated cases in State Hospital, Bremen (Germany) 1908-1922. Complete remissions occurred in	4.8 per cent.
Raynor (1924)	1,004 untreated cases in Manhattan State Hospital 1911-1918. Complete remissions occurred in	3.5 per cent.

Among the so-called mentally improved cases (Table 1) we have included all those who seemed to us to exhibit a definite and unmistakable degree of mental improvement, but in whom either the improvement fell short of what it might have been, or there remained evidence of brain destruction sufficient to preclude the patient's being self-supporting or able to cope with any but the simplest type of environment. As will be observed from Table 1, almost exactly one-half of the total of 156 patients manifested a definite response to the treatment in the form of an abolition of most or of all of their mental symptoms; one feels that the differences within this group of 50.6 per cent. represent differences in the degree of functional restitution, possibly, rather than differences with respect to the efficacy of the therapeusis *per se*.

The unimproved cases are obviously those in whom little or no improvement took place in their mental condition, so that to all intents and purposes they might as well not have undergone the treatment; in addition we have placed in the unimproved group those cases in whom an improvement, although quite definite, was of very brief duration, such as a few weeks or perhaps two or three months.

The percentage of deaths as it appears in Table 1 might at first sight seem rather large. But it must be borne in mind that general paralysis is a disease which results in death within three years in the overwhelming majority of cases. In this connection we may cite the statistics of the New York State Hospitals. These figures (Table 3) show the extreme malignancy of untreated general paralysis: Of 737 cases terminating fatally during 1920, 63 per cent. died during the first year of hospitalization.

TABLE 3

Deaths in Untreated General Paralysis in the New York State Hospitals

Number of paretics dying (1920) in State Hospitals before present treatment methods introduced....	737
Number dying (1920) within 12 months after admission	468
Paretics dying within 12 months after admission...	63%

It is perhaps not surprising, therefore, nor in any way discouraging, that death should be the outcome in 25 per cent. of a group of patients observed for an *average* period of very close to two years and a half. It should be said at once, however, that only half of the number of deaths shown in Table 1 were due directly to general paralysis itself, these deaths having taken place at intervals subsequent to the completion of the course of malaria ranging from three months to three years and one month. It should be noted also that a definite degree of mental improvement actually took place in a few patients who eventually died; and it is therefore interesting to note that in almost all of these patients death took place with relative suddenness,

that is, without a protracted period of physical and mental retrogression. The remaining one-half of the patients who died are those in whom general paralysis itself was not the direct cause of death; these cases died during the course of fever therapy or within two weeks of its termination; hence it may be assumed that the malaria itself was the direct or indirect cause of their demise. From a careful analysis of our material, we feel that it can be conclusively stated that the deaths in 12½ per cent. of this series of cases were more or less directly associated with the malaria fever itself. This matter brings us to the second question—the drawbacks and dangers inherent in the malaria treatment.

The drawbacks to the malaria treatment are principally those which arise from certain difficulties in maintaining the malarial organism in an active state for transmission to new patients as they present themselves for treatment. Since it is next to impossible to keep the plasmodium alive in an artificial culture medium, it is necessary to carry the malarial blood directly from donor to recipient in an unbroken sequence; for which reason it is indispensable that the supply of candidates for treatment should be sufficiently numerous to make this consecutively possible. Clearly, no escape from this difficulty is practicable unless one substitutes for the malarial plasmodium an organism which can be kept alive in laboratory animals, such as, for example, the spirillum of relapsing fever or the spirochæte of rat-bite fever.

A somewhat analogous difficulty is that which arises from the fact that certain patients seem to possess at least a partial degree of immunity to malaria, if we may make such an inference from the observation that in a noticeable proportion of patients (perhaps roughly one in six) the clinical manifestations of the infection spontaneously cease to appear after one or two up to as many as six or eight febrile paroxysms. In still other patients, although these are somewhat exceptional on the whole, it appears impossible to produce malarial infection at all, even after

repeated inoculations with blood which transmits the infection successfully to patients inoculated simultaneously; and we might add that in our experience it has been all but impossible to produce malarial infection in negro subjects. In these less susceptible individuals it is obvious that fever may be produced instead by means of vaccines or relapsing fever or rat-bite fever.

The question of malaria as a direct or indirect cause of death is a much more difficult and troublesome one, and is not made less so even by the realization that general paralysis is ordinarily an inevitably fatal disease, so that the Hippocratic aphorism, "for extreme diseases, extreme methods of cure," is applicable to it with peculiar aptness. And there is moreover the question of the use of malaria in that other and non-fatal form of parenchymatous neurosyphilis, tabes dorsalis. Yet certainly benign tertain malaria does not rank as a cause of death of any importance in those regions of this country in which malaria is endemic.

It has seemed to us that several factors may be operative in causing malaria to end fatally in a higher percentage of patients with general paralysis than would ever under ordinary circumstances be the case. The first among these considerations is the fact that many patients with general paralysis, especially at the stage of advancement to which they have progressed at the time of admission to a state hospital, are considerably under par physically, often having lost an appreciable amount of weight, and giving evidence of having suffered for a year or more previously from a systemic disease. Secondly, an appreciable proportion of our patients are well past the age of 40 when they receive treatment, whereas those who acquire malaria in a region where the disease is endemic would on the whole be more likely to have their first attack at a considerably earlier age. It is a fact that our young patients, almost without exception, have seemed to experience no difficulty in coping with the malarial infection; on the other hand, we have had several patients well past the age of 50 in whom no untoward results have

occurred. Thirdly, it appears to be a well-established fact that a very definite proportion of patients with general paralysis have syphilitic lesions of the aorta, even though these are not demonstrable clinically through signs or symptoms; and it is therefore conceivable that this complication may possibly play some part in the inability of certain individuals to survive the course of fever therapy.

These considerations, which are mere possibilities, would seem to indicate that we lack any very concrete idea of the exact nature of the cause of death in these fatal cases.* At all events, Dreyfus of the Frankfurt Clinic has claimed that by interrupting the febrile attacks by giving small doses of quinine he was able to carry through more than 130 patients, mostly tabetics, with only a single death in the entire series. Since almost without exception in our own cases the febrile paroxysms have occurred at daily intervals instead of every other day, we have recently adopted a similar technique of spacing

*The question of the cause of death in malaria has been dealt with in several recent papers in the foreign literature. Seyfarth, for example, found heart affection the cause in 14 per cent.—with coronary blockage, myocarditis, heart muscle necrosis and fatty degeneration. Malarial septicemia accounted for death in 30 per cent. Cerebral cases numbered 55 per cent., the brain showing massing of parasites in the brain capillaries, punctiform hemorrhages, granulomata, and parasitic emboli. Seyfarth, however, was dealing with severe infections of the so-called algid or typhoidal type.

Hoffmann has reported evidences of blood-vessel paresis or paralysis, such as a small monocrotic pulse, pale skin, cyanosis, cold sweat, and pulmonary oedema. He found caffeine useful in combating this condition; and in common with others, we have used caffeine routinely in all our cases from the time of onset of the febrile paroxysms.

Several French writers have reported all grades of degenerative change in the adrenals in fatal cases of malaria, and Paisseau and Lemaire consider the adrenals and the nervous system the most vulnerable organs of the body to malaria.

Anderson believes that since the features of the cold stage of the malarial paroxysm are practically identical with sympathetic adrenal stimulation, the inference is that repeated malarial attacks in rapid tertian succession put a heavy strain upon the sympathetic-adrenal apparatus with various grades of exhaustion of this apparatus as a consequence—and this, indeed, is borne out by autopsy, he states, so far as the adrenals themselves are concerned.

out the attacks, but we cannot as yet say whether or not patients withstand malaria more successfully by reason of these longer intervals of rest and recuperation between attacks, as it might perhaps be reasonable to expect they should.

The third question which we set out to discuss, namely, the permanence of the results which the malaria treatment is capable of producing, can only be answered at present in a provisional sense, for obviously a period of at least ten years must elapse before we can speak of a cure in any strict sense of the word, or before we can even be certain that the clinical remissions induced by malaria are anything more than simply remissions of greater duration than those that occur spontaneously or as a result of other causes.

In the meantime, we may consider briefly the first 34 patients treated by us— those who underwent a course of malaria during the first year of our experience with the treatment, between June 1, 1923, and June 1, 1924; in other words, those who completed treatment between three and one-half and four and one-half years ago.

As indicated in Table 4, three of these patients died during their course of fever. A fourth died of a series of

TABLE 4

The Present Status of 34 Patients Treated More Than Three and One-Half Years Ago (between June 1, 1923, and June 1, 1924).

Died during malaria	4	
Died 2 months after malaria	1	
Died of general paralysis 6 months to 3 years after malaria	4	
Suicide 8 months after malaria	1	
		10
Unimproved and now worse		1
Unimproved and stationary		5
Improved and stationary		2
Full remission with later relapse (after 2 yrs. and 3¼ yrs.)		2
Full remissions persisting to date		14
		34

convulsions one week after his final attack of malaria. A fifth patient died two months after completing his course of fever, and whereas he apparently died of general paralysis, we felt that the malaria had done something to hasten his end. Thus, 29 of these 34 patients were alive three months after the completion of their course of fever. Of these 29, five have since died—one patient six months after treatment, one one year and a half, one two years and a half and one three years and one month subsequent to treatment. The fifth patient, after achieving a relatively satisfactory remission, became depressed and suddenly committed suicide after completing treatment. Hence, subtracting these ten deaths, we have 24 patients still living out of the 34 who completed treatment three and one-half to four and one-half years ago.

Of these 24 patients, six were originally classified as unimproved. They remain unimproved, and five of them have shown no definite evidence of further physical or mental deterioration up to the present time. Though the practical value of such an outcome is nil, it would nevertheless seem as though the malaria treatment had actually arrested the disease process in these patients or at least in some of them, even though at a stage where any degree of functional restitution was no longer possible.

Two other patients, originally classified as moderately improved, continue to maintain this status at the end of three years and one-half and three years and three-quarters, respectively.

Sixteen of these patients achieved a complete remission and were discharged from the hospital, but have been kept under observation ever since. Fourteen of these 16 patients have shown no evidence whatever of receding from the maximum status which they attained following the malaria treatment; in other words, their state of complete clinical remission has not only continued unmodified over an interval of three and one-half to four and

one-half years, but shows no present signs in any of these patients of doing otherwise.

Of the 16 patients originally considered to have attained a complete remission, only two have suffered a partial relapse, with return of some of their previous mental symptoms in a relatively mild and modified form; the relapse occurred in one patient after two years, and in the other three years and three months subsequent to treatment. One of these patients regained to a fairly complete degree his previous status at the end of about six months, and this without any further treatment. The other patient regained to a partial degree his previous status, after a second course of malaria and two courses of tryparsamide of twelve injections each. It might be stated at this point that except for the last named case and two others, none of the patients here reported received any other form of anti-syphilitic therapy, so that the results here presented are almost without exception those obtained by means of malaria treatment alone.

It is rather noteworthy, perhaps, that relapse did not take place in either of these two cases until at least two years had elapsed since treatment; and this does something to confirm our previous impression that the more complete the degree of clinical improvement obtained in these patients, the longer is that improvement likely to last.

At all events, the outstanding fact to which we would call attention is, not only that complete remissions have occurred in about one-third of our total number of cases, but that in 14 out of 16 cases the remission has been maintained unmodified for a space of at least three and one-half to four and one-half years.

There are two further points which are of a certain interest in connection with the results obtainable from the malaria treatment; namely, the type of patient most likely to respond in a favorable manner, and the influence of the treatment upon the spinal fluid findings.

TABLE 5

Therapeutic Outcome in Relation to Clinical Type
(in 84 cases)

	Simple Dementing	Expansive	Manic
Unimproved or Died.....	33	6	0
Definitely Improved	8	3	4
Full Remissions	7	11	12
Total	48	20	16

Table 5 illustrates the relation between therapeutic outcome and the clinical type of the disease as we have observed it in 84 patients who survived the period of treatment by more than three months. As may be noted, only one-seventh, or 14 per cent., of the 84 patients of the simple dementing type achieved a good remission, whereas three-quarters, or 75 per cent., of the 16 patients of the "manic" or hyperactive type did so.

As to the influence of the malaria treatment upon the spinal fluid findings, especially the Wassermann reaction in the spinal fluid, Table 6 illustrates our experience with 47 patients who have now been followed for at least two and one-half years, and who have received no other anti-syphilitic treatment subsequent to malaria. It will be observed that the malaria treatment has had little or no influence upon the Wassermann reaction in the spinal

TABLE 6

Influence of the Malaria Treatment
Upon the Wassermann Reaction in the Spinal Fluid

Spinal Fluid Wassermann	Number of cases	Per Cent.	
Unchanged	19	40	55
Modified (negative with 0.2 cc.).....	7	15	
Much modified (negative with 0.5 cc.)..	11	24	45
Negative (with 1.0 cc.)	10	21	
Total	47	100	

fluid in a little more than one-half these patients, and this irrespective of the clinical outcome. But what is truly striking is that in a little over one-fifth of these cases of general paralysis, the reaction in the spinal fluid has become *completely negative* following upon treatment with malaria alone. This observation has impressed us very strongly, in view of the fact that as regards the spinal fluid general paralysis is the Wassermann-fast condition *par excellence.*

Table 7 presents the clinical outcome as compared with the Wassermann results in these same 47 patients. The lack of parallelism between the two is rather clearly suggested by the fact that in each of the serological groups the number of remissions does not differ very essentially from the number of those in whom only moderate mental improvement or none at all took place.

TABLE 7

Serological Results as Compared with Clinical Results

Spinal Fluid Wassermann	Moderate or no mental improvement	Good Remissions	
Essentially unchanged	10	9	
Modified	3	4	
Much modified	6	5	
Negative	4	6	
	23	24	47

Table 8 indicates the lapse of time required for the malaria treatment to exert its influence on the spinal fluid in those 28 cases in which the strength of the Wassermann

TABLE 8

Interval Between Completion of Treatment and Modification of Spinal Fluid Wassermann Reaction

Interval subsequent to malaria necessary to attain degree of modification now present	Modified	Much Modified	Negative	Total
One year	3	2	1	6
One and one-half years	1	4	2	7
Two years and over	3	5	7	15
	7	11	10	28

reaction in the spinal fluid become modified subsequent to treatment (Table 6). Clearly, two years is more or less the minimum interval required by rather the majority of cases to attain at least the higher degrees of modification.

A final word about the influence of malaria on the pathological process in the brain in cases of general paralysis. Dr. Ferraro, of the Institute staff, has undertaken a study of this question on a series of 30 brains of patients who died during or after the fever treatment. This study has shown that the inflammatory exudate in the brain is frequently reduced in amount, and in association with this there is also a reduction in the neuroglia reaction. One is, therefore, justified in saying that in many of the brains studied, the microscopic picture shows a marked recession of the pathological process, a finding which can be regarded as evidence of healing in the sense that the inflammatory reaction becomes less active and tends to subside. Tissue that has been destroyed can of course not be restored.

In conclusion we should like to emphasize once again the fact that the patients dealt with in this communication were, almost without exception, definitely psychotic at the time they came under our care; that is, they exhibited outspoken mental symptoms such as necessitated their commitment to an institution for the insane. We

can scarcely help thinking, therefore, that the considerably earlier treatment of these patients would have produced a notably larger proportion of therapeutic results of the maximum order; it is certainly conceivable, for example, that irreparable cerebral damage might have been forestalled by more timely treatment in at least some of these patients, and that many of those who manifested definite mental improvement might thus have been brought within the group of full remissions. It is for this reason that we urge the treatment of these patients before outspoken mental symptoms have announced their presence; and we believe that for this purpose advantage should be taken of a form of treatment now shown to be remarkably effective against a disease which has largely resisted the therapeutic methods of the past. To continue to use the ordinary anti-syphilitic remedies once it appears probable that the patient is suffering from neurosyphilis of the parenchymatous type, is in our opinion a waste of time and opportunity.

Summary

1. Of 156 male patients with general paralysis who received the malaria treatment between June 1, 1923, and August 1, 1927, at least 50 per cent. manifested a definitely favorable response, even though in one-third of these latter residual evidences of previous cerebral tissue destruction precluded full recovery in a clinical sense.

2. In this group, observed over an *average* period of two and one-half years, the death rate due to general paralysis has been 12.5 per cent.; based on the averaged expectation of life of 1.5 year exhibited by untreated general paralytics in the New York State Hospitals, the death rate in the present group would have been at least 65 per cent.

3. Of 34 patients treated more than three and one-half years ago (prior to June 1, 1924), 29 were alive three months after the completion of their course of fever; of these 29, 5 have since died, 6 are unimproved (although

only one of these has definitely retrogressed), 2 have remained moderately improved, and 16 attained full remissions, in 14 of whom their state of complete clinical remission has thus far continued unaltered.

4. In a group of 84 cases, 12 out of 16 patients of the "manic" or hyperactive type achieved full remissions, as compared with 11 out of 20 of the expansive type but only 7 out of 48 of the simple dementing type who did so.

5. In a group of 47 patients followed for at least two years and one-half, the malaria treatment had little or no influence upon the strength of the Wassermann reaction in the spinal fluid in 26 (55 per cent.). But in 10 patients (21 per cent.) the Wassermann reaction has become *completely negative* (to 1.0 c.c. of spinal fluid) following upon treatment with malaria alone.

6. Two years was more or less the minimum period of time required by the majority of cases to attain at least the higher degrees of modification of the Wassermann reaction in the spinal fluid.

7. Since advantage can now be taken of a form of treatment demonstrably effective against a disease which has largely resisted the therapeutic methods of the past, the early recognition of neurosyphilis of the parenchymatous type becomes mandatory.

II.

CLINICAL RESULTS FOLLOWING MALARIAL THERAPY IN GENERAL PARESIS

CHARLES W. STONE

Cleveland

Since the early reports of Wagner von Jauregg on the treatment of general paresis by malarial inoculation, nothing in our therapeutic armamentarium against this disease has created an equal degree of interest. Contributions to

the published literature on this subject have been numerous both at home and abroad. The results reported have varied, but, in general, the earlier reports were enthusiastic, and the more recent ones somewhat more guarded, although still of a favorable character. Several proposed hypotheses have been suggested regarding the mode of action of the malarial and kindred inoculations in general paresis, but, as yet, no generally accepted explanation of the favorable results obtained is available.

On the neuropsychiatric service of Cleveland City Hospital this form of therapy has been studied for the past three years. This service runs upwards of one thousand new psychiatric admissions of various forms of mental disorder per annum. As this psychopathic hospital is intended for the diagnosis and care of acute mental disorders, it receives to a considerable extent the earlier manifestations of mental disease. In most of the cases of general paresis in this series, the acute mental symptoms had developed recently, although a careful history of the individual patient frequently elicited a previous gradual change in personality extending back over months or even years. However, from the standpoint of hospital patients, this group comprises as early forms of general paresis as may be expected to be encountered. The period of observation of these patients in our own hospital averaged between three and four months. Those patients requiring longer periods of hospital supervision were transferred to the Cleveland State Hospital. Through the coöperation of the social service section of our psychopathic hospital, and through the courtesy of the superintendent of the Cleveland State Hospital, we have been enabled to maintain a limited follow-up of our cases, whether they went to their homes or received further institutional care.

At this time we report upon 151 cases of general paresis who have been given malarial inoculations and have responded with typical paroxysms. The results upon the first 101 cases have been reported previously.* This former

*Ann. Clin. Med., June, 1927, v:1119.

report is supplemented by the results observed on an additional 50 cases similarly treated in the past year. The diagnosis of general paresis was made on the basis of the accepted physical signs and mental symptoms of this disease, and in all instances was corroborated by serologic examination of the blood and spinal fluid, and the determination of the cellular and globulin content and the colloidal reaction of the spinal fluid. The ages of the patients inoculated ranged from twenty-four to sixty years; under thirty years there were 14 cases; from thirty-one to forty years were 56 cases, from forty-one to fifty years were 61 cases, and from fifty-one to sixty years were 20 cases. Males numbered 128, and females 23.

The strain of malarial plasmodium used throughout the series was obtained originally from a patient with naturally acquired malaria who was on the medical service of the Cleveland City Hospital. Blood smears showed the presence of two chronological groups of parasites of the double tertian type. Inoculation was made directly from patient to patient, usually with from 5 to 10 c.c. of blood. When made intravenously (the method of choice), as was done in 93 cases, the incubation period was about four and a half days; when made subcutaneously, as was done in 58 cases, the incubation period was about ten days. The number of paroxysms averaged twelve for the entire series. Some patients withstood the malaria much better than others, so the number of paroxysms produced was a purely individual problem. In some cases marked weakness, anemia or slight jaundice developed after a varying number of paroxysms, and such factors aided in the decision as to when the malaria should be terminated by the administration of quinine. Determinations of the blood urea were closely followed, because experience showed that an increase to 80 mgm. or more per 100 c.c. of blood was an indication for the cessation of the paroxysms. Likewise blood pressure readings sometimes provided useful indications for the limitation of the malarial chills. In general, after the onset of malarial paroxysms the trend of the blood pressure is downward, although with individual

paroxysms there may be a temporary rise. A decided fall in blood pressure from its original level, accompanied by signs of physical weakness or threatened collapse, naturally suggests the desirability of terminating the malaria.

In this series, before malarial inoculation, the Wassermann reaction on the blood was positive, and on the spinal fluid was positive or anticomplementary; after the malarial therapy, no marked effect upon these reactions was observed, although we have two recent reports on former patients, one from a family physician and one from a hospital, of negative Wassermann reactions on the blood. After malarial therapy the cellular content of the spinal fluid usually has diminished, and in some instances has come within normal limits. The globulin content of the spinal fluid has likewise diminished as a rule, and frequently the colloidal reaction has shown some lowering of the curve. In the cases where improvement has occurred to the extent that the patients have resumed work, the cell count of the spinal fluid has been reduced generally to 10 or less per c.mm.; the globulin to a trace; and the colloidal curve has become less pronounced, being reduced from the paretic to the luetic (tabetic) zone. There has been no constant parallelism between these changes in cellular and globulin content and colloidal reaction. In some instances there was a tendency of these reactions to return to their former levels. This seemed particularly true in those cases which have not shown clinical improvement. Such cases have shown some diminution in cell count and globulin content within a month after malarial inoculation, with at least a partial return to their former levels within the succeeding one or two months. The colloidal curve has shown a tendency to become less pronounced than before malarial inoculation, but this has not been so marked as in the cases which have shown clinical improvement. These changes in the spinal fluid, therefore, may be of some value, along with other evidences of improvement, in estimating the prognosis in individual cases.

During the period of malarial paroxysms and immediately thereafter, the general resistance of many paretics is much lowered, as is evidenced by the fact that at this time the patients are particularly susceptible to the development of various forms of infection of the skin and subcutaneous tissue, ranging from localized furuncles to extensive fatal cellulitis, and of pulmonary infections such as bronchopneumonia.

In a few instances after malarial inoculation, some improvement has been noted in the speech, and some diminution observed in the tremor of the face and tongue, together with some lessening in the activity of the deep reflexes. In only one instance have pupillary disturbances disappeared, and this did not take place for many months, during which time active antiluetic treatment was given.

The extent and degree of improvement in the mental state of patients may be inferred from the fact that of the 151 so treated 77 have returned home, and of these at least 34 are working steadily; 47 others are still (November 1st, 1927) in the Cleveland State Hospital. Of these 47 cases, 6 are showing improvement, 24 show no change and 17 are growing worse.

The remaining 27 cases have died. Six deaths followed the development of extensive cellulitis; 5 deaths were from bronchopneumonia and one was from empyema; two died following apoplectiform seizures which occurred during the period of malarial paroxysms (both of these patients had had previous convulsive seizures); one died with signs of exhaustion and emaciation shortly after the termination of his malarial paroxysms; 12 deaths occurred months after the malarial therapy was concluded, and were due directly to the general paresis. It is evident that the malaria *per se* should not be held as the direct cause of the deaths in this series (with one possible exception), yet, through lowering the resistance of certain patients, already diseased, to other infections, it served as an active contributing factor in some of the deaths. It is of interest to note that in the last 50 cases treated there have been but

three deaths. One of these deaths was the empyema noted above; one was from bronchopneumonia; and one occurred in an individual who showed a poor response to the malaria, and had a spontaneous cessation of paroxysms after six chills. He was transferred to the Cleveland State Hospital where death later took place. Three deaths among 50 cases compare most favorably with the 24 deaths among the previous 101 cases. The explanation, we believe, is largely dependent upon two factors: First, a careful selection of the patients to whom the malaria should be given; all paretics otherwise diseased were excluded; only those were selected who appeared strong and reasonably well nourished. Second, a careful individual nursing service during the period of paroxysms and for a couple of weeks thereafter; this is of importance in the agitated form of paresis because it is this group of patients who are so likely in their excitement to acquire abrasions of the skin which later may develop into serious infections, or who from undue exposure may contract pneumonia; and it is likewise important for the inactive paretic because it provides a means of better maintaining his resistance through adequate food and general bodily care.

Comment

Twenty-three of the last 50 cases inoculated with malaria also were given tryparsamide. We have been disappointed in finding no appreciable difference in the physical condition, the neurological signs, the mental symptoms and the changes in the blood and spinal fluid in this group when compared with the 27 other cases not given this combined therapy.

After malarial inoculation, in our experience, favorable results may develop gradually over a period of several months. If such results are not observed within six months, a reinoculation with malaria may be considered. We have observed several instances of marked improvement following such reinoculation. This would seem particularly applicable in those cases which show decided

improvement in their physical condition after malarial therapy without a corresponding change in their mental condition.

After malarial inoculation, a maniacal paretic may quiet down to such an extent as to become an easily handled institutional case, even though the mental state does not clear up sufficiently to warrant his return to his home.

In our series we have no evidence that general paresis has been cured by malarial inoculation, even though there is good evidence of marked improvement having taken place in a large percentage of the cases. Accordingly, it is natural to expect some relapses of the mental condition to occur. We have had 5 instances of such relapse which has necessitated resumption of hospital care.

Summary

In a series of 151 cases of general paresis treated by malarial inoculation, and observed for a sufficient period of time to permit drawing conclusions concerning the results, 27 have died, 77 have improved sufficiently to live at home, and of these 34 are working steadily; 6 have improved but still require institutional care; 24 show no improvement, and among these are 5 who have improved and later relapsed; and 17 are progressively growing worse.

Conclusions

After malarial inoculation in general paresis, the percentage of patients showing improvement, conservatively estimated, is sufficiently high to warrant consideration of this method as a form of therapy in this disease. It is to be hoped, however, that malarial inoculation against paresis may serve as a step in the development of a more satisfactory form of therapy with a less empirical basis. The mortality rate encountered indicates that the malarial treatment of general paresis cannot be undertaken lightly. Malaria lowers the resistance of patients, already diseased, to other forms of infection. This fact should suggest the

desirability of exercising a careful selection of the cases to whom this form of treatment may be administered. Improved nursing care for patients given malarial inoculation is important as a means of lowering present mortality records. Favorable results after the use of this form of therapy may not be seen for several months.

III.

EXPERIENCES WITH MALARIAL INOCULATION IN SYPHILIS

JAY F. SCHAMBERG

Philadelphia

I will not attempt to give you any statistical study of the cases which I have had under my observation, for it would be in large part a duplication of the figures which have been presented to you by the previous speakers. I think there is a remarkable concordance of results throughout the world with respect to malarial treatment of paresis and of tabes dorsalis.

With regard to paresis it would seem that in about one-third of the cases there is a complete remission, and in one-third more a very considerable benefit, and one-third unimproved. And these figures seem to be corroborated by reports from various parts of the world. I will perhaps with your permission, content myself with reference to a few cases of special interest.

The number of cases under the observation of Dr. Greenbaum and myself is considerably less than that of the previous speakers. We treated nearly seventy cases, and this included paresis, tabes dorsalis, cerebrospinal syphilis, and a few cases of congenital syphilis in adults. One case of a paretic, thirty-five years of age, private patient, who had classic serologic and clinical evidence of the disease is of interest. He went through fifteen paroxysms of malaria. Before the treatment was instituted he was violently manical, had to be restrained hand and foot in bed.

At the end of the malaria treatment he was perfectly rational, and after his convalescence left the hospital for his home elsewhere, and for the past two years has been pursuing his usual vocation as a civil engineer giving entire satisfaction. One year after the treatment there was complete negativity of the blood Wassermann which is quite an achievement, because, as Dr. Kirby has remarked, the blood Wassermann and the spinal fluid Wassermann are ordinarily irreducible with the ordinary methods of treatment. His spinal fluid Wassermann was moderately positive, a typical paretic gold curve had changed to a luetic gold curve. A second case is somewhat unique as far as I can make out from the literature. A man of fifty-six with a chronic cerebrospinal lues, fixed pupils and strongly positive blood Wassermann and strongly positive spinal fluid findings sustained upon very slight provocation a fracture of a metatarsal bone of the foot, which did not heal. Later decalcification of the surrounding bones developed which was thoroughly studied by a number of orthopedists. Numerous roentgenograms were taken and it was finally pronounced that he was suffering from an arthropathy. This lasted for some months. He had previously had all sorts of approved luetic treatment.

In view of the fact that he had had so much treatment without influencing his serologic findings, I recommended the use of malarial inoculation. He went through a very nice course of malaria and within a very short time the fracture healed; he was able to walk first with a cane, and later without a cane, whereas, at the time of the first visit he was on crutches; subsequent X-ray pictures of his foot showed a complete recalcification, a complete restoration of structure; the orthopedists now state that it is impossible to differentiate between the bones of the two feet.

This case is of particular interest I think because it suggests the advisability of the use of this method of treatment in early syphilitic arthropathies.

The third case is that of a man thirty-four years of age who had had quite an adequate early treatment for his

syphilis, but his blood Wassermann remained strongly positive. Spinal fluid Wassermann showed a strong positivity with a suggestive paretic curve; in view of this fact we subjected him to malarial inoculation. He went through a course of some twelve or thirteen paroxysms. After that his neurasthenic condition and his loss of sexual power improved, and he took on some twenty pounds in weight. I think my colleagues of this evening, if they were to dwell on this subject would inform you there is often a marvelous improvement in the well-being of paretic patients and others after malarial treatment.

This improved condition was maintained for a year. At the present time he has a strongly positive spinal fluid, a very weakly positive blood Wassermann, and a suggestively paretic gold curve. There are no mental symptoms whatsoever to-day. His neurasthenic symptoms have disappeared. He contemplates marriage and wants our advice upon the subject. Here is a man who, it seems to me, it is advisable to reinoculate with malaria if we can. This brings up the question of the indications for the employment of malarial inoculation. In advanced paresis after a very considerable degree of degeneration has taken place, it is obvious that all one can hope for is improvement, perhaps arrest; in many cases no improvement whatsoever will be achieved.

The most ideal results should be achieved in the early cases of paresis, or preferably, in the pre-paretic state. In those cases in which a patient after an adequate antisyphilitic treatment shows a persistently positive spinal fluid Wassermann and other pathological alterations in the fluid, malarial inoculation should be tried.

Some two years ago I had the opportunity while in Vienna of being shown by the late Professor Kyrle a series of records of patients whom he had treated with malaria, patients in all stages of syphilis. He was treating early syphilis as well as late syphilis, treating it even in the early primary stage after a preliminary course of six neosalvarsan injections, and the treatment followed by six

neosalvarsan injections. He told me that he could count the relapses upon the fingers of one hand and his series of cases covered fifteen hundred inoculations.

Now, the significant thing about his records was this (and he showed them to me at random): Patients who had had persistently positive spinal fluid Wassermanns, more or less latent cases, that had received all sorts of approved luetic treatment, without any change in the serologic findings would show negative reactions in the spinal fluid in from six to nine months after malarial treatment in a very high percentage of cases. This was quite striking, and it is the opinion to-day of some of the best German syphilographers, that malarial inoculation should be employed in this very condition in patients who, after energetic courses of antisyphilitic treatment, show persistently positive spinal fluid Wassermanns, before any nerve symptoms develop. That is the ideal stage in which to treat these patients, for in the majority of cases they are still relatively young men, and fairly robust, and the risk of malaria in such cases is less than in the well advanced cases of paresis.

Now, there is a certain risk with malarial treatment, as has been emphasized by the previous speakers. Some men have been more fortunate than others with their cases. The fatality depends a good bit on selection. In our seventy cases we were fortunate enough to have only one death and that was in a paretic. But a great many of our patients were not paretics. And furthermore none of them were asylum cases, although some quite well advanced.

Again, when you come to treat private patients with malaria you will find that it is a most disturbing and distressing method of treatment to apply. The hardened, lowest stratum of asylum cases may perhaps not complain of suffering, but when you get more sensitive patients who have been bred in greater luxury, you will find that the high fever, the severe chills, the drenching sweats, the accentuation of all previously existing pains and the development of new ones will be bitterly complained of, and it

is not a method of therapy to be lightly taken up, apart from any danger that may be attached thereto.

Now, as has been stated, there is no constant parallelism between the serologic and the clinical improvement. In some you will get a negative blood Wassermann, and spinal fluid Wassermann with little clinical improvement and in other cases quite the reverse may take place. What is most significant of all is the marked regression in the pathologic picture as has been commented upon by Dr. Kirby. Nearly all of the histologists who have examined the brains of paretics who have received malarial treatment are in accord that there is a remarkable change in the microscopic picture to such an extent in many cases that it would be impossible to identify the brains as those of a paretic, and indeed it is quite astonishing to histologists that such a degree of pathologic regression or restoration can take place; even more significant is the fact that in the vast majority of cases in which an opportunity has been given to examine the brain carefully for spirochætes after malarial inoculation they have been found absent. I believe it is generally held that in about 33 per cent. of brains of paretics it is impossible to find spirochætes. But a competent histologist will find them in the remaining cases.

Bielchowsky, Kirchbaum of Hamberg, two observers from Vienna, Straussler and Koskinas, and more recently, Freeman of Washington, have in the aggregate examined almost one hundred brains most carefully and in not a single instance were they able to find spirochætes. Forster of Germany, however, in examining several cases did find spirochætes in one instance.

A very interesting case was related by Jahnel of Munich who did a cerebral puncture upon a case of paresis and found numerous spirochætes. The patient then developed a purulent pleuritis and ran a high temperature for several weeks, finally succumbing. A most painstaking study of the brain failed to reveal spirochætes. This observation has almost the force of an experiment.

Now, the very interesting point has arisen and was touched upon by Dr. Stone, as to the therapeutic mechanism of malarial inoculation in paresis. From the time of Hippocrates and Galen down to Boerhave and Sydenham through to the present time, there have been instances of patients suffering from various psychoses that were improved or arrested through some intercurrent febrile disease. It was a review of this literature that started Wagner-Jauregg upon his fever inducing experiments.

It will be realized that there was no particular specificity in the fevers, but various fevers brought about these results. I should state that the dominant opinion held today chiefly by European observers is that the fever induced is not the prime cause of improvement. Many hold the view that in some way malaria brings about certain antibody production which is noxious to the spirochætes. Others hold that the death of the malarial parasites produces some protein substance which stimulates the defensive mechanism of the body.

We have endeavored in our Research Institute to carry out certain experiments with a view to shedding light if possible upon this very complex question. We have been able to prevent syphilis in the rabbit by giving the rabbit a series of daily very hot baths, four days after intratesticular inoculation of a spirochætic emulsion.

I may add that in some 5,000 syphilitic inoculations in rabbits, as I recall, we have had 100 per cent. successes in inducing syphilis. If these animals receive a hot bath, 113° Fahrenheit for about fifteen minutes on eleven successive days no syphilis develops, no clinical evidence of syphilis, no syphiloma of the testicle, and furthermore if the femoral and popliteal glands are removed several months later and inoculated into other rabbits, which is a necessary procedure to prove failure of infection, these inoculations are negative.

We were enabled too to produce a rapid healing of a secondary syphiloma with fifteen baths, almost daily, excluding Sundays, and with an average rise of temperature

in the rabbit of from 4° to 5° Fahrenheit. Chancres heal as quickly as if you had given them a curative dose of arsphenamine. The spirochætes disappear within a few days. It is quite striking to note the rapidity with which these chancres heal up under hot baths.

Now, of course, this simply shows that the elevation of the body temperature of the rabbit has a healing effect upon rabbit syphilis. It does not indicate whether the effect of the heat is direct or indirect. In order to throw some light upon this question we subjected spirochætes suspended in physiologic salt solution in a test tube to heating upon a water bath.

We carried out three separate experiments of this kind now covering a period of a year and a half or more. In the first experiment, the spirochætes heated to 40° or 41° Centigrade, about 104° to 106° Fahrenheit, for an hour and a half failed to induce syphilis in the rabbit, although at the time of inoculation the suspension under the dark field microscope showed numerously active organisms. They were in some way biologically damaged or paralyzed so they were later unable to produce their disease effect.

In a second series of experiments we did not obtain exactly the same result, but a very interesting one. A series of some twelve rabbits was inoculated and twelve kept as controls. That is, they were inoculated with the unheated spirochætes. The latter all developed syphilis within eighteen to thirty-six days, that is, developed a syphiloma of the testicle containing spirochætes.

But those infected with heated spirochætes within thirty-six days were entirely free, but thereafter from the thirty-sixth day to the eighty-eighth day they began gradually to develop a syphiloma with the presence of spirochætes. Two of them developed the lesion upon the eighty-eighth day. In this experiment the period of incubation was greatly lengthened.

In a third experiment which is about terminating we confirmed the first one. In other words, the animals have

not developed syphilis during an observation period of over one hundred days. Certain precautions are necessary in this experiment. One must not have any large particles of testicle in the spirochætic emulsion because it may not be permeated by the degree of heat employed. One must not pour from the test tube, but pipet the solution out with a pipet because the upper wall of the test tube may contain spirochætes clinging to it which are not subjected to the degree of heat which is registered by the thermometer. I may say the gland transplantations from these rabbits have likewise remained negative.

It would seem from this experiment and from certain others that have been carried out that the spirochæte is extremely thermolabile. If you heat the spirochæte to 105¾° Fahrenheit, for six hours, its motility begins to cease and it breaks up. This is a much lower degree of heat than is necessary to destroy ordinary bacteria.

These rather interesting experiments upon the rabbit suggested to us the trial of very hot baths in the treatment of human syphilis.

It is rather interesting to observe that in almost all countries, patients for some centuries suffering from syphilis have migrated to thermal springs. We have our own hot springs here in the United States. In Japan they have some noted springs at Kusatsu where the natural temperature of the water is extremely high and patients there get into water at a temperature of 121° to 123°; after becoming accustomed to it they can stand this temperature for a few minutes; it is said that these springs are particularly curative for patients who are losing their noses, which suggests to most of us syphilis.

We have been able to produce a temperature from 102° to 103° to 106°, in human beings by means of hot baths without any material danger. The patient has an ice cap upon his head and special appliances are employed to keep the temperature at a given point. The temperature of the water is about 112° or 113° increased gradually; the

maximum temperature is only maintained for fifteen minutes, although the patient is in the water for about forty-five minutes.

We have treated early syphilis by this method in order to determine what it would do. We have noticed the disappearance of the secondary eruption. We observed the disappearance of superficial tertiary eruptions. We have observed a quantitative reduction in the strength of the Wassermann reaction upon which we would not insist too much.

One would hardly expect the use of hot baths by raising the body temperature in the human being to have the same curative influence on syphilis as malaria. It is not our expectation that such would be the case. But we are endeavoring to determine whether the use of extremely hot water associated with other methods may not abbreviate the period of disappearance of symptoms and bring about negativity of the Wassermann test more rapidly and thus constitute an adjunct or aid in the treatment of syphilis. We observed some side effects which were rather interesting. There is a brief leukocytosis followed by a reduction in the white cells, a slight rise in the systolic blood pressure with a marked fall in the diastolic blood pressure, almost to zero at times. There is, on the average, a 10 per cent. increase in the blood sugar and a 10 per cent. decrease in the cholesterol. The uric acid and urea of the blood are unchanged. There is no change in the proteolytic or lipolytic enzymes in the blood.

Whether this method of treatment will have any place in the therapy of syphilis is a question which can only be determined by further observations and study, and whether any other fever inducing method will serve to act as a substitute for malaria can only be determined by further study. The intravenous injection of typhoid vaccine by bringing about a sharp rise of temperature to a very considerable height has given interesting results, but unfortunately the period of fever is not sufficiently protracted.

In malaria we have a rise of temperature of very considerable degree for a period often of six hours continuously, whereas with the injection of foreign proteins or drugs designed to raise the body temperature the rise of temperature is very brief. That must be taken into consideration in adopting substitute methods. There can be no doubt, I believe, and it is the general consensus of opinion, that the results achieved from malarial inoculation in paresis have exceeded those which have been obtained by other methods. Paresis was the one stumbling block in the progress of our treatment of syphilis. Various remarkable advances had been made but despite all these advances, despite the introduction of the newer drugs, paresis was still the malign and ultimate outcome in many cases.

But it does seem now as if methods are at hand whereby paresis may be improved, may be perhaps arrested, and who knows, may be cured. If we may judge from the remarkable change in the microscopic picture and if we may judge from the fact that in Vienna some of the paretic patients are well and working after six, seven or eight years, and some of Dr. Kirby's cases are apparently well and working at the end of three or four years, it is only the future which will enlighten us as to the ultimate verdict.

A Symposium on the Use of Antipneumococcic Refined Serum in Lobar Pneumonia[1], *December 15, 1927*

I

THE CONTROL

(ABSTRACT)

JESSE G. M. BULLOWA

A. THE IMPORTANCE OF A CONTROL SERIES OF CASES [2]

The evaluation of the effect of any therapeutic procedure in pneumonia is attended by certain inherent difficulties. Probably seven of every ten patients recover regardless of treatment, and therefore if one chances upon a succession of favorable cases, he is apt to attribute the benefit to the special treatment then in use. A short series of fatalities, unless carefully controlled and analyzed, may lead to a condemnation of what is really a very useful procedure.

Refined concentrated serum is desirable in order that the dose may be small and readily administered without severe reactions. It is desirable that it be polyvalent (several sera may be mixed) because the pneumonias resulting from pneumococci of different serological types may be indistinguishable at the onset. Because no one can foretell with certainty the cases which may develop adequate protection in response to the pneumonic invasion, the benefit from treating patients is best discovered by comparing the results in a series of serum treated cases with a similar series treated without serum.

At Harlem Hospital each alternate patient with pneumonia is placed in the serum series. It is not practicable

[1] These researches were financed by Mr. Lucius N. Littauer through the Littauer Pneumonia Fund of New York University in association with the Influenza Commission of the Metropolitan Life Insurance Company and the Research Laboratory of the Department of Health, New York, N. Y.

[2] The clinical studies are from the Medical Service, Harlem Hospital, Dr. Lewis K. Neff, Director.

Dr. Louis I. Dublin and the staff of the Statistical Bureau, Metropolitan Life Insurance Company, tabulated the data.

to alternate the cases according to type on admission as this might occasion a delay of many hours or days. The injection of a powerful polyvalent serum of Types I, II and of a less potent Type III assures prompt treatment of the cases selected for serum.

We accept and retain as pneumonia patients those having pneumococcus infections of the lung with definite lobar involvement, as evidenced by unmistakable physical signs, fluoroscopy, or radiography.

Except for the serum, all patients are given the same medical care in respect to drugs and nursing, in accordance with a definite plan.

B. Data Necessary About the Cases Before One is Capable of Judging the Effect of Serum

On admission cases are rated in accordance with a definite plan. The rating assumes 100 to be health and for each of five catagories a maximum of 20 may be subtracted.

Respiratory: Involvement. Rate. Pleurisy.

Nervous Condition: Headache. Irritability. Sleeplessness. Delirium. Apathy. Coma.

Circulatory Efficiency: Rate. Cyanosis.

Gastrointestinal: Distension. Vomiting.

Complications. Special Factors.

In our series studied during the past year we had 401 cases of lobar pneumonia, of which 28 were rejected because it was impossible to type them, and 8 because of concurrent febrile diseases, such as scarlet fever, tuberculosis, etc.; 365 remain to be studied, 169 in the serum series and 196 in the controls; 220 were rated.

In a general way the rating on admission indicated chances for recovery. The Type I cases treated were sufficiently numerous to classify as good, fair and poor. Chart (5). Of 6 patients rated poor (below 50) we saved 2 patients with serum, while we lost all treated without serum;

of those rated fair (50 to 70), we saved 4 of 6 in the serum group against 6 among 11 without serum. We saved with serum some very ill patients who might have died without it.

Many have maintained that the excellent results reported with serum treatment in hospitals have been due to the early hospitalization rather than to the serum. For both Type I and Type II serum series the mortality among both early and late cases was less than for the controls.

Not only did the serum treatment appear to reduce the number of deaths but it shortened the illness of those who recovered. Certainly this was advantageous, as it meant a saving in hospital care and of subsequent invalidism.

With serum we not only saved more patients and shortened the illness of those who recovered, but apparently the serum delayed death in those who perished, just as occurs in animal experiments.

When we combine all the cases early and late by types, and study the effect of the serum, it will be noted that Type I and Type II for which we had potent sera, showed fewer deaths per hundred among the serum treated cases. The greater benefit from early treatment has been revealed on charts already shown.

C. Size of Series Requisite

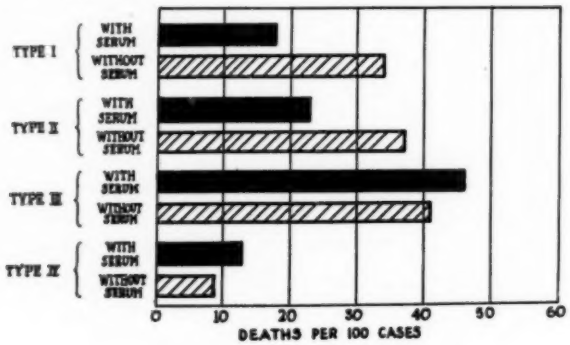
Naturally, as physicians, we considered how long we were justified in continuing to deprive patients in the control series of what may be a valuable and available therapeutic aid. In spite of the fact that we were impressed, as the research proceeded, by the beneficial results of the serum, the question arose as to whether there was conclusive proof that the serum is of value. What test can we apply to our data to see whether proof is adequate and how can we determine the number of cases necessary for a judgment? This leads us into a brief digression into what differences in results is statistically significant, and the meaning of the standard error.

Without going into technical details, it may be explained that the relative spread, or flatness, of the curve of occurrence of a quality is measured by what is called the standard error of the measurements. In order that the difference between measurements in two separate materials, *e.g.*, case fatality of two similar hospital populations with pneumonia, one of which received serum, shall be recognized as definitely significant, the distance between the peaks of the two curves must satisfy a certain statistical test. The difference between the average measurements in the two cases must be at least equal to twice the "standard error" of the difference. Whenever this ratio falls below 2, we are not in a position to judge whether any significant meaning is to be attached to the difference.

Deaths per 100 cases
Pneumonia patients treated (A) with Serum and (B) without Serum
Harlem Hospital, September, 1926 to October, 1927

DEATHS WITHIN 24 HOURS OF ADMISSION EXCLUDED

Type	(a) WITH SERUM			(b) WITHOUT SERUM			Difference in Case Fatality (a-b)	Ratio of Difference to its Error
	Cases	Deaths	Deaths per 100 Cases	Cases	Deaths	Deaths per 100 Cases		
Type I	55	10	$18_{\pm}5.2$	53	18	$34_{\pm}6.5$	$-16_{\pm}8.3$	1.9
Type II	26	6	$23_{\pm}8.3$	38	14	$37_{\pm}7.8$	$-14_{\pm}11.4$	1.2
Type III	24	11	$46_{\pm}10.2$	17	7	$41_{\pm}11.9$	$5_{\pm}15.7$	.3
Type IV	54	7	$13_{\pm}4.6$	82	7	$9_{\pm}3.2$	$4_{\pm}5.6$	.7



In the Type I cases we have practically obtained a result which is twice the standard error, 1.9. A greater difference in the percentage recovery of treated cases than those untreated may be accomplished by future improvements in the serum, and by earlier administration. Even though the serum were to remain as it is and the difference in the results the same as at present, 16 per cent., a greater number of cases would reduce the standard error and carry conviction of the value of serum treatment. When, for Type I pneumonia, the ratio of the difference in per cent. fatality between serum and non-serum treated cases to its standard error, becomes more than two or three, it will be our duty to administer serum in all Type I cases and urge its administration on others.

To evaluate the result of a treatment in pneumonia, there are required adequate comparable series with and without the treatment. We believe we have obtained such series by the devices adopted—alternating patients and rating them on admission. The size of the series requisite is determined by a consideration of the standard error.

II.

THE RELATION OF BACTERIEMIA IN LOBAR PNEUMONIA TO PROGNOSIS AND SERUM THERAPY

MILTON B. ROSENBLUTH

Blood cultures were made on 500 patients with lobar pneumonia. The statistics were analyzed from the standpoint of prognosis and serum therapy.

As to the incidence of bacteriemia in lobar pneumonia, investigators have reached widely divergent conclusions. Some, such as Prochaska and E. C. Rosenow, have reported positive blood cultures as occurring with great frequency, the former having found them in 100 per cent. of a series of 50 cases, the latter in 91 per cent. of a series of 175. On the other hand there are many who find positive blood cultures in a relatively small percentage of their

cases. Notable among these are Schottmueller, who reports 23 per cent. as positive in a series of 227, and Cole and his co-workers at the Rockefeller Hospital, who report 27 per cent. as positive in a series of 728. The probable explanation of this disagreement as to the incidence of bacteriemia lies in a difference in the type of clinical material studied and in the employment by one group of certain refinements such as the elaboration of laboratory technic and the taking of more frequent and larger quantities of blood, which were not employed by the other group.

Using a simple routine hospital technic in which 3 c.c. of blood were divided among two hormone agar plates and one tube of broth in a dilution of one to ten, we obtained positive blood cultures in 35 per cent. of Type I cases, 31 per cent. of Type II cases, 25 per cent. of Type III cases and 7 per cent. of Type IV cases.

As to the prognostic value of a positive blood culture there is a remarkable lack of unanimity and the reason for this seems to be closely related to the question of incidence. Those investigators who report a high incidence of bacteriemia have invariably attributed little or no prognostic value to it, while those who report a low incidence regard it as a very serious prognostic sign. I believe this is due to the fact that the separation of cases by blood culture findings into positive and negative groups is too arbitrary and ignores the degree of bacterial invasion which is really the more important factor. If sufficient blood were used and the cultures were made at short intervals it is probable that all or most cases would yield positive blood cultures. But the significance of a few bacteria thus demonstrated should certainly be distinguished from a bacteriemia readily shown in 1 or 2 c.c. of blood.

Comparing the mortality in patients with positive blood cultures and with negative blood cultures we found that in Type I, 16 per cent. of the negative blood culture cases died while 81 per cent. of the positive blood culture cases died. In Type II, 21 per cent. of the negatives died while 75 per cent. of the positives died. In Type III, 17 per cent.

of the negatives died while 85 per cent. of the positives died. In Type IV, 8 per cent. of the negatives died while 100 per cent. (only three cases) of the positives died.

Furthermore, the incidence of positive blood cultures in the fatal cases was more than twice as great as the incidence in the recovered cases.

Early in our work we were strongly impressed with the fact that our statistics taken in the usual manner, comparing mortality rates for treated and control cases, by type, did not adequately express the efficacy of the serum as it appeared to us at the bedside. We had often observed in patients who appeared very profoundly stricken, the most impressively favorable results. This observation and the common knowledge that serum will frequently render the blood stream free of bacteria led us to inquire more closely into the relative effectiveness of the serum in the cases with bacteriemia and in those without it. We hoped in this way to obtain more exact data as to the indications for treatment, and as to the better selection of those cases in which serum was apt to be most effective.

On comparing the results of our treated cases with those of our untreated, we found that in Type I the mortality of untreated cases, which was 37 per cent., was reduced in the treated cases to 21 per cent., a reduction of 43 per cent. In Type II the mortality of untreated cases, which was 40 per cent., was reduced in the treated cases to 26 per cent., a reduction of 35 per cent. While these figures are impressive, they do not appear to have been sufficiently convincing even in Type I cases, to interest the medical practitioner in the use of this form of therapy.

However, in the cases with positive blood cultures, the effect of serum treatment appears to be much more strikingly shown. In Type I, 81 per cent. of the untreated cases died, whereas 39 per cent. of the treated cases died, a reduction in the mortality of 51 per cent. In Type II, 75 per cent. of the untreated died, while 38 per cent. of the treated died, a reduction in the mortality of 49 per cent., which is almost as great as that effected in Type I.

The question then arises whether the effect of the serum is limited entirely to those cases in which a bacteriemia is present, or whether there is benefit also in the absence of bacteriemia. On examining the results in the negative blood culture cases, we find in Type I untreated cases a mortality of 16 per cent., while in treated cases the mortality is 11 per cent. The reduction here is much less marked than in the Type I positive blood culture cases. In Type II negative blood culture cases, treated and untreated, the results are identical, 21 per cent. mortality.

In order to compare the effect of early and of late treatment in the bacteriemias, we separated the cases into those admitted during the first three days of their illness, and those admitted later. In Type I the mortality in late cases was 42 per cent. while in the early cases it was 11 per cent. These figures suggested the importance of instituting serum treatment at the earliest possible moment. But in order to determine whether it was the serum treatment or merely early hospitalization which accounted for so marked a lowering of the mortality in the cases treated early, we studied the untreated cases in a similar way. In these cases, however, we found no such difference between patients admitted early and those admitted late. In Type I the late cases had a mortality of 80 per cent., while the early cases had a mortality of 85 per cent. In Type II the late cases and early cases had an identical mortality, 71 per cent.

From the results of these studies, we particularly urge the use of serum in all cases showing a bacteriemia. In Type I and Type II the evidence in favor of serum appears to be convincing. In Type III bacteriemias we cannot recommend serum with the same assurance, but the prognosis here is so nearly hopeless that it would seem proper to give the patient the slight chance which serum has to offer. With the more potent sera which have been prepared of late, this may not be so forlorn a hope as heretofore. In Type IV cases with bacteremia, we feel very strongly that patients should be treated with a polyvalent

serum of Types I, II and III, because of the possibility that the typing has been incorrect.

I believe we are justified in drawing the following conclusions:

1) In untreated cases with bacteriemia of such a degree that it can be demonstrated in 1 or 2 c.c. of blood the prognosis is definitely bad.

2) Type specific serum is indicated in *all* cases, but particularly in those with bacteriemia. In the negative blood culture cases it is indicated to prevent bacteriemia.

3) All Type IV cases with bacteriemia should be treated with serum because of the possibility that they may later prove to be Type I or Type II cases.

4) Serum treatment should be instituted at the earliest possible moment.

5) The effect of serum on fatality appears to be exerted largely on those cases showing a bacteriemia, cases without demonstrable bacteriemia being benefited relatively little.

III.

THE METHOD OF ADMINISTRATION AND THE DOSAGE OF ANTIPNEUMOCOCCUS SERUM IN LOBAR PNEUMONIA

WILLIAM H. PARK and MISS GEORGIA COOPER

If a serum is available that can be safely given intravenously, then it should undoubtedly be so given and the whole amount of antibody be made immediately available instead of waiting for its gradual absorption which requires a period of one to two days for its completion. If, however, one is afraid to give the refined or unrefined serum intravenously, it is useful but less so if given intramuscularly. The effect of the rate of absorption on the time when the antibody is available is shown in the chart.

The number of doses: The first injection should be large, but before we can speak intelligently of dosage we must agree on a unit of antibody. This we have done with other sera where it was possible to adopt standardized units, as in diphtheria and tetanus antitoxins. No intelligent person would now approve of giving the dose of diphtheria antitoxic globulin solution as so many c.c. instead of so many units.

During the past year the Felton polyvalent preparations which we have used have varied as follows:

Type I antibody between 300 and 2000 units per c.c.

Type II antibody between 100 and 1000 units per c.c.

Type III antibody between 10 and 200 units per c.c.

If these refined preparations of antipneumococcus serum had been simply labelled polyvalent pneumococcus antibody we would in some cases have given unwittingly 1/6th of the Type I antibody and 1/10th of the Type II antibody to some that we did to others. If the refined or unrefined polyvalent serum is to be used extensively in the future, as we hope and believe it is, the Hygienic Laboratory should require the units for each type for which it is recommended to be stated on the package just as it is now for diphtheria, tetanus and scarlet fever antitoxins. If the Federal Government does not see its way clear to do this, the physicians themselves should demand it. Nothing will be more effective in causing the biological plants to perfect their methods and to eliminate the horses producing a serum weak in antibodies than such a demand.

A unit is the amount which protects mice from an average of a million minimal fatal doses of very virulent pneumococci.

In toxic cases of pneumonia the antibody matching the type of pneumococcus causing the pneumonia is quickly neutralized, partly or wholly, by the specific soluble substance while the antibodies in polyvalent sera specific for the other two types are but slightly affected and decline slowly as in a normal person. The amount to be given a

case of lobar pneumonia depends on the duration and severity of the disease, as these indicate in a general way the amount of toxic or immune substance probably present in the body.

Any case in which a pronounced bacteriemia has developed will need much larger amounts than one in which the blood is sterile. This is the reason why a late or severe case needs as a rule much more than an early severe case. The amount of antibody needed in some cases is very moderate in amount, in others it is large and in a few it is beyond our possibility of giving.

In order to clarify our ideas as to the amount of antibody required to neutralize all the pneumococcus specific poisonous substance, blood was taken from eleven late toxic cases to be tested by Miss Cooper. Five of these were Type I pneumonia cases and six Type II. Of the Type I cases, in one, there were traces of antibody in the serum; in one, there were traces of specific toxic substance; in two, the toxic substance in 1 c.c. of each of their bloods neutralized 1 unit of antibody and in the fifth, 1 c.c. neutralized 5 units. This would mean that in two of the toxic cases we would require about 10,000 units and in the most toxic cases about 50,000 units to neutralize the specific toxin in the body at the time of giving the injections.

In the six late and very sick Type II cases, the blood of two contained but a trace. In the blood of two others the toxic substance required one unit of antibody per c.c. of blood and each of the remaining two required the enormous amount of 50 units of Type II antibody.

The dosage required for the two most toxic cases would be approximately 500,000 units, which would require 500 c.c. of our present Type II refined serum. These cases entered the hospital late and had septicemia; one did and the other did not receive serum and both died.

Our opinion as to dosage is as follows: Every case should receive on admission as nearly as possible 10,000 units of Type I antibody and of Type II antibody. As

soon as we have available a potent No. III antibody in the serum the same quantity of units should be given. As soon as the case is typed, if the temperature remains high or if septicemia or bacteriemia is shown to be present, the injections of a monovalent or polyvalent serum should be continued every eight to twelve hours. If the pneumonia is due to Type IV pneumococcus, it is well to stop with the third injection. The antibody for these types assembled as Type IV is still so feeble that it is not wise to draw upon the moderate amount of antibody solution available. The same rule applies to Type III cases, for although we have a potent serum against our old laboratory Type III cultures, it is ineffective as yet against the freshly isolated cultures and so is probably of little value in treatment.

If the temperature after dropping rises again above 102° the injections should again be given unless abundant antibodies are shown to be present in the blood or the temperature is known to be due to complications such as serum sickness, pulmonary abscess due to the streptococcus or other conditions for which we would not expect any advantage from the antibody injections. Methods such as the quick macroscopic agglutination test of Arlyle Noble should be used when possible to detect an abundance of antibody in the blood. If this is present it is wasteful and unnecessary to continue the injections. When unrefined serums are used the number of units in each dose may have to be reduced because of fear of the deleterious effects of such large injections of serum. Within a year or two a plentiful supply of refined serum should be available.

Papers Delivered at the Annual Meeting
January 5, 1928

ON THE SIGNIFICANCE OF BACTERIAL ALLERGY IN INFECTIOUS DISEASES

HANS ZINSSER
Boston

The General Principles of Bacterial Allergy

Although the early studies of Koch [1] and his associates on superinfection in tuberculosis and the physiological effects of the injection of tuberculin into infected animals constitute a definite observation on bacterial allergy, this type of hypersensitiveness is less clearly understood than are other phases of this general subject. In the reaction of the animal body to coagulable proteins much has been learned about the mechanism, and we are reasonably well informed concerning the relationship of protein anaphylaxis to antibodies. Generalization from the study of protein anaphylaxis to other forms of hypersensitiveness, at first hoped for, has met with many obstacles, chief among which has been the difficulty of repeating the experiments on passive sensitization with antibody-containing sera which has been the backbone of our understanding of true anaphylaxis. Largely because the mechanism of the antigen-antibody reaction has not been clearly demonstrable in such forms of hypersensitiveness as hay fever and asthma, reactions to animal emanations, certain food idiosyncrasies and the drug idiosyncracies, some immunologists have advocated an entire separation of these conditions from the phenomena of anaphylaxis proper. This view, which was at first advocated by Doerr and is still upheld by many immunologists in this country, has neglected basic similarities in favor of discrepancies which in our opinion do not represent so much fundamental differences of principle as they do gaps in our experimental knowledge.* And these gaps are gradually being bridged by accumulating

*These views have been very thoroughly discussed in a paper on "Hypersensitiveness" by the writer published in the *Boston Medical and Surgical Journal*, 1927, cxcvi:387.

experimental and clinical evidence. We have maintained for a considerable number of years that all forms of specific hypersensitiveness are probably based on the same fundamental mechanism—namely, an acquired altered capacity of the cells to react to the particular inciting substance, in which the varying chemical and physical nature of the antigens is responsible for certain differences in the apparent mechanism, especially as regards the appearance of demonstrable circulating antibodies.*

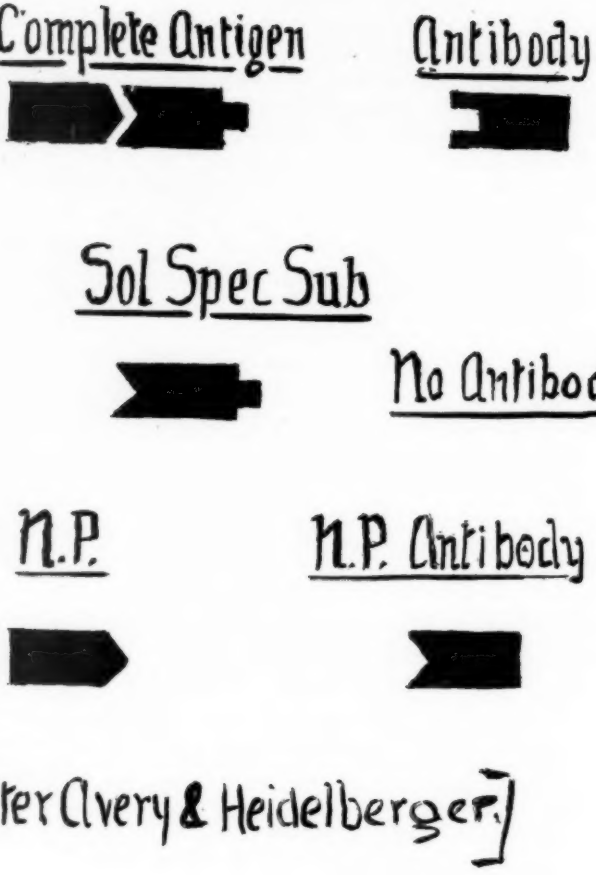
To consider the mechanism of bacterial allergy, which, incidentally, has not been solved in anything like an adequate manner, would lead us into long and difficult discussions quite out of place in a paper intended to elucidate clinical relations. It will be profitable, however, to outline the present state of experimental knowledge as far as it seems to us pertinent.

The logical approach to the problem is a consideration of modern knowledge of the bacterial antigen recently acquired by the correlation of chemical analysis with functional properties. We know now, from the work of Avery and Heidelberger,[2] as well as that of our associate Mueller, and ourselves,[3] that if we immunize an animal with whole bacteria—either living, formalinized or killed in some other manner that avoids dissolution of the cell substance—we obtain antibodies which are type specific and bring about the well-known test-tube reactions of agglutination, precipitation, opsonization, etc. If the bacteria are subjected to even the most gentle chemical cleavage—indeed, even to such mild changes as autolysis or its probable analogue, solution by bile (which is feasible in a limited number of them)—the bacterial antigen may be split into at least two antigenically functional fractions; one, a nitrogenous nucleoprotein-like material, the other,

*Our opinions as to a needed modification of the prevalent conception of antigenic substances have been stated in a paper on the bacterial antigen by the writer and Mueller which is to appear in a series of immunological papers to be published under the editorship of Professor Jordan of Chicago, under the title of "The Newer Immunology."

a partial antigen, probably of carbohydrate structure, which has been called the "soluble specific substance" by Avery and Heidelberger, the "residue substance" by ourselves. We will adopt, hereafter, the terminology of Avery and Heidelberger, because we think the term better chosen as more descriptive. The antibodies which are produced by the injection of the whole bacteria will react specifically by precipitation with the soluble specific substance, but the soluble specific substance injected by itself will not cause antibody formation of any kind and is manifestly, therefore, a sort of haptophore group which is present in the whole bacteria and lends them other specific properties. Immunization with the nitrogenous nucleoprotein material will produce antibodies, but these antibodies are of a different kind from those produced by the whole bacteria and are less restrictedly specific, representing a loose species specificity rather than a type specificity.

We published these views with Tamiya in 1926, in the same number of the *Journal of Experimental Medicine* in which, to our great satisfaction, an entirely corresponding analysis was published by Avery and Heidelberger, whose graphic illustration of the conditions follows:



[After Avery & Heidelberger.]

A type of the precipitation reactions by which these facts are shown to apply to bacteria other than the pneumococcus is taken from our paper with Tamiya:

	Serum H. Rabbit injected with formalinized pneumococci	Serum I. Rabbit injected with bile-dissolved pneumococci	New York State antipneumococcus serum
Nucleoprotein			
Concentrated	+++	+++	
1:5	++	++	+++
1:10	++	++	+++
1:20	++	+	+++
1:50	++	±	++
1:100	+	±	++
1:200	+	—	+
1:400	—	—	±
Residue			
Concentrated	++	—	Not done.
1:5	++	—	" "
1:10	+	—	+++
1:20	+	—	++
1:50	—	—	+
1:100	—	—	—
1:200	—	—	—

(From Zinsser and Tamiya *J. Exper. Med., loc. cit.*)

It is of the greatest importance to remember in connection with the further development of our subject that these two fractions, loosely united in the whole bacteria, tend to dissociate most easily, mere solution being sufficient to disrupt them, but attempts to put them together again have so far been unsuccessful.

It has been known since the early observation of Koch on superinfection and the tuberculin reaction, and subsequent studies of a similar nature on the mallein reaction, on the typhoidin reaction (by Gay [4] and his associates) and, recently, on a considerable number of organisms in which are included staphylococci, the hemolytic streptococci and others, that in the course of an infection, or after recovery, animals and men may become hypersensitive to the infectious agent, and subject to intracutaneous reactions similar in principle, though less marked than the well-known tuberculin reactions.

The study of these phenomena has yielded a certain number of definite facts which we can best illustrate by taking our examples from the tuberculin reaction itself. Such "bacterial allergy," as it is called, does not develop, as Baldwin [5] pointed out many years ago, without tissue reactions in the form of tubercles. It was for a time believed that tuberculin allergy was an infection rather than an injection reaction, in the sense that an animal did not react unless he were infected with living organisms. It was shown a long time ago, however, by Prudden and Hodenpyl [6] that dead tubercle bacilli could give rise to tubercles, and some years ago the writer with Petroff [7] definitely confirmed the fact that animals can be rendered allergic by the injection of dead tubercle bacilli, provided that tubercles resulted from the injections. Indeed, such allergy could be produced with tubercle bacilli that had been boiled, and a relatively small dosage sufficed to bring about the condition.

It is clear, therefore, that Baldwin's dictum "No tuberculin reaction without a tubercle", or —in other words— without inflammatory tissue reaction, is still valid, even though it is immaterial whether the inflammation is in response to living or to dead organisms.

If guinea-pigs are treated systematically and for a long time with the nitrogenous fraction of tubercle bacillus extracts they do, indeed, develop a form of allergy; but this is quantitatively far less marked than when dead tubercle bacilli, or the unfiltered extracts containing bacterial fragments are used.

Such dependence of the fully developed allergic response upon tissue reactions is so clear and invariable that it must be interpreted as a fundamental premise. Yet, in spite of the essential nature of the tissue reactions in the genesis of the allergic response, the specificity of the reactions, in the sense that tuberculin hypersensitiveness follows in its full development only stimulation by the presence of tubercle bacilli, indicates that the stimulus

itself, though requiring tissue reactions to be allergically effective, must originate in the bacteria themselves. We are thus confronted with three facts, which must be coordinated: First, that it is the presence of the tubercle bacilli which incites a specific reaction; next, that the antigenic stimulus is not released from bacilli except by the presence of tissue reactions; and, thirdly, that the injection of chemically produced tubercle bacillus cleavage products which, because of their solubility, fail to incite tissue reactions, are not capable of eliciting more than a feeble allergy.

These facts have puzzled immunologists for a long time and have led to much experimentation that has included the injection of extracts of tubercles (Bail,[8] Lange,[9] Zinsser and Tamiya, and others) and the treatment of animals with extracts of normal tissues and inflammatory tissues from sources other than tuberculosis. In 1921 our own experiments[10] convinced us that the tuberculin reaction had no relationship to the ordinary agglutinating, etc. antibodies; and that it was distinct from the typical anaphylaxis which, by sufficiently prolonged efforts, can be induced in animals with bacterial proteins. It is this fact which explains the failure of so many to produce passive sensitization to tuberculin with the serum of animals immunized with tubercle bacilli. Many of the theories which have been advanced to explain the tuberculin reaction, and which have depended upon the conception that a toxic substance is split from the tubercle bacilli by immune sera have remained unsatisfactory.

In seeking for light on the subject, we turned, a few years ago, to the study of allergic reactions with other bacteria, in which both chemical cleavage and antibody production were more simply and easily attained. We worked with typhoid bacilli, staphylococci and hemolytic streptococci, all of which yielded a certain amount of information; but we obtained what we believe a reasonable clue to the mechanism by studies with the pneumococcus. This organism—as everyone knows—autolyzes readily in culture

and in suspension, and is easily dissolved in bile—a process which, with Atkin, [11] we are inclined to interpret as merely a speeding up of spontaneous solution.

Briefly outlined, our experiments indicated that young guinea-pigs that do not react normally to intracutaneous injections of whole pneumococci, pneumococcus extracts, or pneumoccus autolysates, can be powerfully sensitized if they are treated with whole pneumococcus cultures or with pneumococcus autolysates. While a number of methods of sensitization, all of them depending upon the injection of the whole organism or the products obtained by some method of autolytic solution will sensitize, the final severe and typical skin reaction can be elicited only if autolysates produced either by standing or by treatment with bile, are intracutaneously administered. Guinea-pigs properly sensitized—and the sensitization may be accomplished in as little as six or eight days—may give a feeble reaction to the nucleoproteins produced by alkaline extraction and acid precipitation or by injection with dead whole pneumococci, but will react powerfully if injected with autolysates of the pneumococcus.

These experiments, taken together with the preceding facts, seem to us to indicate a definite line of reasoning which is supported by further knowledge elicited in connection with the fate of tubercle bacilli in the tuberculous animal. Many workers in this country, notably Manwaring and Bronfenbrenner, [12] have occupied themselves with intraperitoneal lysis of the tubercle bacillus, a form of dissolution of the bacilli which so far it has been impossible to produce in the test tube. Though the actual occurrence of extensive bacteriolysis of the tubercle bacillus has been questioned by many workers, the likelihood of the liberation of specific products from bacilli thus injected into the tuberculous animal is encouraged by the important—and in this connection, pertinent—experiments of McJunkin. [13] These we have on several occasions successfully reproduced, and though it is not easy to obtain them, we consider them accurate observations. McJunkin injected tubercle bacilli into the peritoneal cavities of tuberculous

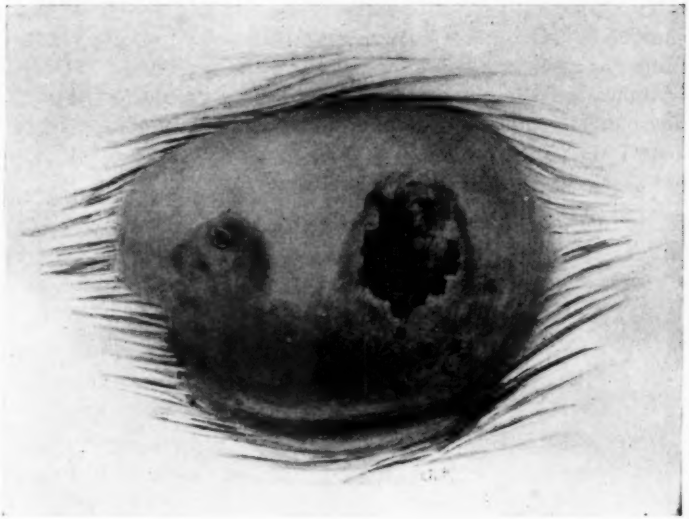


FIGURE 1.—The reactions on a guinea pig sensitized with the pneumococci. Point A, shows area around injection of pneumococcus autolysate on September 22nd. Point B, showing hemorrhage and necrosis with much edema sagging downward, shows a similar injection of pneumococcus autolysate made on the following day, September 23rd.

(From Zinsser and Grinnell—Further Studies on Bacterial Allergy, *J. of Bacteriology*, xiv, No. 5, 1927.)

guinea-pigs, removed the exudates just before death and filtered them free of bacteria. When he treated normal guinea-pigs with such filtrates, eight or nine days after a series of injections, these guinea-pigs would react with a more or less typical allergy to intracutaneous doses of O. T. McJunkin conservatively leaves it undecided whether he sensitized actively or passively, but putting all the facts together, we think it clear that he sensitized actively with bacteria-free materials and thereby made an important contribution to the understanding of bacterial allergic reactions.

If we consider all of these apparently uncoördinated facts in their proper connection, they seem to us to point in a definite direction, and in order to indicate this clearly, we will recapitulate them before drawing our conclusion.

(1) Specificity of the tuberculin reaction forces the assumption that, whatever the mechanism, the stimulating substance or antigen must emanate from the bacilli.

(2) Tuberculin allergy develops in guinea-pigs within two or three weeks after the injection of living or dead bacilli.

(3) Its development as the result of the injection of dead bacilli excludes the participation of a soluble exotoxin as a necessary part of the mechanism.

(4) It develops in a typical manner only when tissue reactions (tubercles) are formed around injected bacilli or fragments, and does not develop in its complete form when chemically prepared extracts of tubercle bacilli are administered.

(5) Nevertheless, the injection of filtrates of peritoneal exudates in which the body cells and fluids of a tuberculous guinea-pig have acted upon the bacilli induce typical allergy (McJunkin).

The coördination of these facts can have only one meaning—tuberculin allergy is a reaction stimulated by a specific product of the tubercle bacillus body, an antigen

which is potently liberated in the inflammatory foci under the influence of tissue reactions, probably by a process of lysis. These conditions can be imitated intraperitoneally, as in the McJunkin experiments, but attempts at chemical extraction of this antigen are never completely successful, probably because—as Gideon Wells has often pointed out—even the most careful chemical manipulation is apt to denaturize the biological properties of cellular substances. It is most likely this factor which has rendered our understanding of bacterial allergy so confusing, and has led to so many initial errors on the part of all who have investigated the problem. Our own experiments with the pneumococcus bear out the above interpretation, since here—with an organism that readily undergoes autolysis in the test-tube—we found that such a biologically produced solution of the bacteria gave rise to reactions comparable in severity to typical tuberculin reactions, whereas none of the chemically produced pneumococcus substances gave anything more than an incomplete reaction in sensitized animals.

Thus, bacterial allergy becomes a simple immunological reaction in which characteristic development and typical reaction depend upon an antigen which cannot be produced in its full functional activity except by the gentle biological process of lysis or autolysis.

The final proof of this conception still awaits *in vitro* autolysis of tubercle bacilli and other organisms—an accomplishment in which, so far, we have failed. But, lacking this final link, it seems to us reasonably clear that in bacterial allergy we are dealing with the sensitization of the body by autolytically liberated antigenic substances which are absorbed from any focus in which bacteria react with inflammatory tissues, and as a result of which the body is rendered subsequently sensitive to contact with these same autolytic products, whether they are liberated and absorbed from a chronically existent focus, or from an identical infection subsequently acquired.

From a clinical point of view this train of occurrences, for which ample experimental evidence exists, must needs have far reaching consequences. It can hardly be questioned that a body which is allergic to a given bacterial antigen is vulnerable to a degree that may lead to serious pathological change. For it may be easily seen that the skin reactions in tuberculous animals, in guinea-pigs injected with abortus bacilli, in rabbits and guinea-pigs injected with streptococci and in properly sensitized pneumococcus animals may be accompanied by inflammation, extensive edema, hemorrhagic transudation, and even necrosis.

Allergy and Tuberculosis

The significance of bacterial allergy in tuberculosis has been the objective of a long series of investigations begun, in principle, by Koch in his studies on superinfection. The subject has been excellently reviewed, from a slightly different point of view, by Long [14] in an article published last year. Though Long deals particularly with the development of methods of immunization, he discusses at some length the view that the allergic state is"nothing more than a rapid mobilization of the same forces which operate in the normal animal." This view, though rediscovered by many of us, is obviously suggested by the observations of the earlier workers and frequently expressed in one way or another. Lowenstein [15] devotes an entire section to this subject in his article on "Immunity in Tuberculosis" and quotes von Behring himself, Escherich and others as having favored this view. Even in Calmette's [16] recent experimentation, the keynote is the effort to produce and maintain a positive tuberculin reaction, which is regarded as evidence of resistance. It means, in the case of tuberculosis, that active immunization can probably not be achieved without the production of positive reaction to tuberculin—and the tuberculin reaction cannot be induced in animals, as Baldwin stated many years ago, without the production of the foci spoken of as tubercles. And since tubercles or, at any rate, the cytological and perhaps

serological reactions coördinated with them, can be produced only by the administration either of living or of dead tubercle bacilli, these are the only two methods of active immunization that need be seriously considered at this time.

When the writer with Petroff [7] proved, a few years ago, that active tuberculin reactivity could be produced by the injection of dead tubercle bacilli, it naturally suggested itself to attempt immunization by first inducing allergy in guinea-pigs in this manner, then to infect these animals —together with a parallel series of controls. Experiments carried out in this manner by Ward and Jennings with the writer [17] on a not inconsiderable number of animals were as favorable as it was reasonable to expect them to be, when animals as susceptible to tuberculosis as guinea-pigs were employed. Others have obtained negative results. But it is worth noting that Petroff and Stewart [18] Boecker and Nakayama [19] and Nasta and Ionesco [20] have further confirmed the observations of Petroff and ourselves on the sensitizing effects of killed tubercle bacilli, and that Langer [21] and Fedders [22] have succeeded in thus sensitizing children. Moreover, Petroff and Stewart have confirmed our own results on the relative immunity conferred by dead tubercle bacilli in guinea-pigs and Petroff is repeating this work on a larger scale. In all the work—our own as well as that of most of our predecessors—the underlying idea has been that the mechanism opposing superinfection is essentially allergic; and that such allergy means that the body is on a hair-trigger as it were, to respond with an energy far more strenuous than the normal reaction to the attack of the specific invader. It may well be that the method of Calmette, who uses living bile-attenuated cultures, may eventually prove more effective than the methods based upon the use of dead tubercle bacilli. Should this be the case, we venture to predict that such advantages will be due to its greater capacity for inducing tuberculin allergy. On the other hand, since Petroff has

recently shown [23] that Calmette's B.C.G. contains organisms which are capable of inducing a progressive tuberculosis in guinea-pigs and is therefore not, in the proper sense of the word, "avirulent," this very capacity for allergy production may be based on a more considerable extension of its pathological effects than at first suspected. And since we know of our own experience that tuberculin allergy can be produced with no inconsiderable intensity, and can be reasonably maintained, by the repeated administration of dead tubercle bacilli, we believe that this method should be more fully exploited before the more dangerous methods are too widely employed.

Allergy and Scarlet Fever

The interest that has of recent years been in evidence regarding bacterial allergy in general has included the study of streptococcus infections, and in 1925 Dochez and Sherman [24] and the writer with Grinnell [25] published studies in which sensitization with streptococcus cultures and with filtrates of the so-called "Dick toxin" was carried out. The two studies were essentially alike. In our own work, sensitization was most successful when the whole bacteria were injected, but other streptococcus products —including the Dick filtrate—likewise induced sensitization. It was of considerable interest that the most potent reactions on reinjection were obtained with the Dick filtrates, which are analogous to tuberculin, in that they represent a filtrate of cultures in which a certain amount of autolysis may be regarded as having taken place and which is both heat stable and allergically active. This assumption, moreover, is rendered more likely by the recent work of Duval and Hubbard [26] who find that the culture lysate produced from scarlatinal streptococci *in vivo* is a more potent antigen than the ordinary culture filtrate.

The chief differences between our earlier studies and those of Dochez and Sherman [24] consisted in the fact that they were able to neutralize the allergic antigen by the use of antiscarlatinal serum. We did not succeed in this,

as we had failed previously in many attempts so to neutralize tuberculin with antitubercle bacillus sera made by many different methods. However, we did only a few experiments in this direction, and used only guinea-pigs, whereas Dochez and Sherman worked both with guinea-pigs and rabbits, with this point particularly in view. Studies which we are carrying out at the present time are aimed at further elucidation of this point, and in rabbits it is relatively easy to produce streptococcus allergy by all the methods of sensitization mentioned above, and to obtain reactions which are not unlike the ordinary Arthus phenomenon in its milder manifestations. A recent article which deals particularly with allergic reactions carried out with streptococci of erysipelas and scarlet fever by Dochez and Stevens [27] confirms the earlier studies regarding both the production of the allergic state and neutralization with serum, and in its further developments to some extent explains the discrepancy between our own earlier failures to neutralize and the success obtained by Dochez and his collaborators. Dr. Grinnell and I found that guinea-pigs, after having passed through a susceptible phase, passed into an insusceptible one, which we interpreted as the possible sequence of an immune condition upon a hypersusceptible one, a suggestion which encouraged our attempts to neutralize. The last study by Dochez and Stevens deals chiefly with rabbits, in which the conditions of allergy are in some respects fundamentally different from those prevailing in guinea-pigs. Their observations, however, are explanatory of many irregularities which they and we have observed. They find that their animals pass through several consecutive periods: One of sensitiveness, which follows the first incubation time and during which the animals display a cutaneous sensitiveness which can be neutralized with serum; following this a second period of hypersusceptibility supervenes, during which no neutralization is possible; finally the animals again become insusceptible.

Dochez and Stevens interpret their results as lending considerable likelihood to the suggestion recently made

by Bristol [28] that the rash and the clinical symptoms of scarlet fever may be due to allergic sensitization to the products of the hemolytic streptococcus. They call attention to the fact that in early infancy intracutaneous injections of the scarlatinal filtrates are usually negative, and Cooke [29] adds to this the important observation that the blood serum of such negatively reacting infants has no neutralizing power. This is entirely analogous to observations made by Grinnell and myself on the insensitiveness of young guinea-pigs to pneumococcus autolysate, in that the serum of such animals has absolutely no neutralizing power for the antigen when applied to naturally or experimentally hypersusceptible animals. It is therefore at least important to consider the possibility that sensitization to an organism which so frequently invades the human throat may take place and may thereby give rise to an allergic condition to which many of the manifestations of scarlet fever could be attributed.

Moreover, this, too, would explain why hemolytic streptococci, which are found in so many human infections and all of which, in the recent studies of Mackie [30] and of Smith [31] seem to be capable of producing toxic substances entirely analogous to those produced by the scarlatinal variety, fail in so many cases to give rise to generalized skin eruptions and systemic injuries associated with the classical, clinical picture of scarlet fever.

Such a conception adds to rather than detracts from the importance of the observation made by the Dicks. For it would seem that, in the Dick toxin, we are confronted with an entirely new type of bacterial substance, one which injures the sensitized body, giving rise to symptoms not unlike those to be expected from a primary toxic action; and which, though heat stable and essentially an allergic antigen, is still neutralizable by an antiserum—a mechanism which adds a new and important chapter to the sum of our immunological knowledge.

Bacterial Allergy and Asthma

The relationship between hypersensitiveness and asthma has long been a well-recognized fact, the respiratory symptoms depending upon the manner in which the antigen gets into the sensitive body and establishes its first and most concentrated contact with the tissues of the respiratory system. It is not even necessary to assume relative concentration of the hypersensitive state in these tissues, though this may well be the case when the sensitization itself is acquired by inhalation of the antigen. That all these conditions can be experimentally reproduced has recently been shown by Ratner, Jackson and Gruehl.[32]

On the basis of analogy, therefore, there is no reason whatever to doubt that bacterial allergy may produce similar conditions, provided the proper bacteria gain entrance to or multiply in the upper respiratory tract. Moreover, there are many clinical records of individuals whose asthmatic conditions are in some way related to chronic infection of the accessory sinuses; and there are a few cases on record in which removal of such foci has cleared up the asthmatic symptoms. The indirect demonstration of the etiological connection by skin reactions and desensitization with bacterial materials has been studied particularly by Walker,[33] Frank and Strauss,[34] Koessler and Moody[35] and by Duke,[36] and such investigations have in general supported the idea. It must not be forgotten, however, that such indirect proof is less convincing in the case of bacteria than in that of other antigens, because human beings may be incidentally sensitive to many different bacteria without necessary relationship to an existing asthma. Furthermore, Duke, who thinks these cases are more rare than generally claimed, points out that it is often difficult to distinguish between an allergic reaction and one of actual infection. He also very logically suggests that these cases may be so rare because an individual so sensitized would often be automatically desensitized because of the frequent and prolonged presence of the responsible organisms.

Occasionally direct observations are possible in the case of accidental inhalation of bacterial substances by laboratory workers, and there are probably few laboratories, in which tuberculin is produced or handled in quantity, where severe bronchial inflammation and cough, if not true asthma, has not followed exposure. In our own laboratory a few years ago, when we were concentrating large quantities of tuberculin and unsuccessfully attempting to produce asthmatic seizures by spraying tuberculin into boxes containing tuberculous and normal guinea-pigs, two of us repeatedly experienced severe reactions. In one of us, in a series of three such reactions there were violent systemic symptoms, including rise of temperature and chill, and local respiratory attacks which initiated the seizure, and in one case there was severe coughing and respiratory difficulty, which went on with diminishing severity throughout the attack. The first sign of the condition in this case was irritation and secretion from the nose and trachea, followed by coughing that was sufficiently violent to cause considerable sternal pain. In the other case, the respiratory symptoms were less prominent, but it is interesting to note that though entirely absent during the first attack, they developed during a second attack about three weeks later.

While the proof for the etiological importance of bacterial allergy in asthmatic attacks is not as soundly based as is a similar indication between asthma and other forms of allergy, it would nevertheless constitute a rather astonishing departure from the general analogy if such a condition did not occur.

Bacterial Allergy and Coryza

The condition which is spoken of as the common cold is probably not a clinical entity, and it is not only possible, but likely that a number of etiological factors may produce conditions of this kind. In spite of the fact that most bacteriologists of experience have tried their hands at the elucidation of this condition, it is not even certain at

the present time whether the condition is or is not contagious, and in certain forms of the malady we are personally convinced that the disease can be acquired without contagion. The most noticeable things that strike one in the study of the common cold are, first of all, the large variety of bacteria that have been described at one time or another as responsible, the close similarity of the early stages of every severe cold with the manifestations of allergic conditions such as sensitiveness to pollen, horse dander, animal emanations, etc., and the fact that during the very early stages of the cold the secretions are almost free from bacteria. During the later stages a true bacterial inflammation seems to supersede and then, of course, bacteria are plentiful and their species distribution is dependent to some extent upon the peculiarities of the preexisting flora in the individual. The filterable virus explanation advanced some years ago by Foster,[37] Kruse[38] and others has not been substantiated, and our own attempts to link up the cold with the salivary viruses of Levaditi[39] have been entirely unsuccessful.

Based on the common experience familiar to everyone we have, on three separate occasions, done an experiment which many have done involuntarily at one time or another —namely, brought on a severe cold under conditions which definitely exclude any relationship to extraneous infection. The experiment is simple, and consists merely in taking a hot bath and then exposing oneself to cold air until an uncomfortable chilly feeling is experienced. Such a procedure usually results within twelve hours in the early signs of a severe cold, which runs its ordinary course.

This perfectly definite train of events excludes infection from without and can be explained only by one of two alternatives—either a direct invasion by bacteria previously present on a mucous membrane in which the capillary disturbances due to the chilling have permitted penetration, or by an allergic reaction of a sensitive mucous membrane to the bacterial antigens present in the

nose when the communication between tissues and surface are established by the capillary permeability resulting from the chilling. It is more than likely that human beings are all sensitive to one or more of the organisms present in their respiratory tracts, and that the degree of this sensitiveness fluctuates according to the recently existing local flora. The noticeable similarity of the early stages of such reactions to the allergic conditions mentioned above, the speed of onset and the almost bacteria-free condition of the early exudate in many cases favor in our opinion an allergic mechanism.

After the allergic reaction has been thoroughly aroused it is only natural that a secondary bacterial inflammatory process should supervene.

It is unfortunately impossible at the present time to conceive a crucial experiment which would prove this point of view. If there were, we would not venture to suggest this mechanism without it. On the other hand, this conception is included in our general thoughts on bacterial allergy because we believe that it should lead to a close epidemiological study of colds, such as that now going on at the Presbyterian Hospital, whereby perhaps the question of contagiousness can be settled one way or the other. Such epidemiological studies in the past have been deceptive, because during the season of colds members of a community or family group are all more or less exposed to analogous conditions, and it is not easy to disentangle the variables influencing distribution of the disease.

Allergy and Rheumatism

Clinical evidence has established the association of the conditions of tonsillitis, injuries of the myocardium and of the heart and chorea with the various pathological conditions known as acute and subacute arthritis. The clinical course of what is generally spoken of as an acute rheumatic condition is such that it suggests an infectious etiology, and in the associated conditions of tonsillitis and a limited number of the cardiac lesions bacteria of the

streptococcus group have frequently been found. Yet, though almost all bacteriologists who have had the opportunity to study acute cases have taken frequent cultures from joint exudates and, at autopsy, from pericardial fluid, positive cultural results from these lesions have been the exceptions. We believe, from our own experience on routine cases in a number of different hospitals, from the study of the literature and from reports of persistent and painstaking efforts such as those of Swift and Kinsella [40] that typical articular and pericardial exudates in acute rheumatism are usually sterile, at least so far as such well-known bacteria as the streptococcus group are concerned. If living organisms are present in such joints with regularity, they must belong to some species not cultivable by ordinary methods. The opinion that no actual infection of the joints themselves exists is, moreover, borne out by the clinical course as well as by the pathological sequences, which are quite different from those of joints locally infected with pyogenic organisms.

We believe it fair to formulate from this that, while acute articular rheumatism and associated conditions in their ultimate etiology are very probably bacterial infections, the actual condition of the joints themselves is not the result of local invasion by these bacteria.

As to the underlying bacterial causation, outside of Achalme's bacillus and a few isolated observations in which staphylococci have been found, the majority of investigators—guided particularly by the result of bacteriological studies of throat lesions, foci in the teeth, blood cultures and cultures from valvular vegetations—have continued to attribute rheumatism to some form of non-hemolyzing streptococcus. It is needless to review the long literature of this subject, which has been adequately summarized by Swift [41] in a number of places. There has been no great variation in the manner of investigation, none of the workers finding the organism with any frequency in the joint fluids, many of them finding streptococci of one type or another in blood cultures with a frequency ranging

from the probably normal 8 per cent. of Swift and Kinsella to the over 80 per cent. surely exceptional, experience of Herry.[42] In most cases in which many isolations have been made, such as—for instance—the recent investigations of Small,[43] and of Birkhaug,[44] all but a few of the organisms that were regarded as significant were isolated from the throats and other locations remote from lesions in the joints or the circulation. In this class also belongs a short-chained streptococcus recently isolated by us at autopsy of a case of acute rheumatic infection in which the blood contained a pneumococcus—probably referable to small patches of a terminal infection in the lungs—while the streptococcus was isolated by planting fragments of myocardium—a result which may indicate that so many blood cultures are sterile in these cases because the organisms responsible for the rheumatic condition may be focally located and but rarely discharged into the circulation.

It is not our purpose to go into the interesting subject of a bacteriological analysis of the various types of streptococcus that have been described, except to say that with few exceptions reliable workers have isolated non-hemolytic streptococci belonging either definitely to what is generally spoken of as the *Streptococcus viridans* group or, as in the more recent work, organisms which produced no changes on blood and which may be perhaps most simply described as falling into the Gamma group of Smith and Brown.[45]

In most cases, workers who have isolated such organisms and have further investigated their relationship with rheumatism, have continued their studies by injecting cultures of the particular bacteria into animals, using chiefly rabbits. In many cases they have produced joint lesions in such animals, obtaining pathological changes not unlike those obtained in human arthritis. And, indeed, this is not surprising to anyone who has worked in bacteriology for any length of time, because the development of joint lesions in rabbits injected with any of the usual cocci,

for whatever purpose they may have been injected, is a common occurrence.

Among the most experienced and persistent workers along these lines have been Rosenow [46] and Swift and his co-workers. [47] Rosenow in 1913 began the publication of a series of papers in which he reported upon cases of rheumatism from which he isolated streptococci of the viridans type with many of which he was able to produce joint lesions in rabbits. These lesions in many—though not in all—cases were non-suppurative. Since Rosenow developed a theory of specific localization with which we cannot deal in this paper, it would not be useful to review in detail all of his work..

Swift and Kinsella in 1917 found non-hemolytic streptococci of the viridans group in less than 10 per cent. of the blood cultures taken from rheumatic cases. They found that their organisms did not fall into a uniform group, and concluded that it was not justifiable to speak of a specific *Streptococcus rheumaticus*. While they did not completely deny the streptococcus etiology of the disease, they expressed themselves in a manner that left the entire question open. In subsequent papers Swift and Boots, [47] though chiefly concerned with the influence of salicylates on the joint lesions in rabbits, investigated a larger experimental material which confirmed in point of fact much of the information collected by other workers. Using four strains of non-hemolytic streptococci isolated from blood cultures in rheumatic cases, they produced a large number of joint lesions by various methods of injection. For future reference we wish to call attention to the fact that cultures from the affected joints in the rabbits were positive in not more than 12 per cent. This point will be of considerable interest in our further discussion. Swift and Boots speak of the joint lesions in their rabbits as having "a superficial resemblence to some of the lesions found in patients with rheumatic fever."

These observations of Swift and Boots correspond with considerable accuracy to the earlier work of Rothschild

and Thalheimer,[48] who produced multiple arthritis in about 50 per cent. of rabbits which they injected with—it is important to note—a variety of streptococci, including viridans, so-called rheumaticus and hemolytic strains, as well as a culture from the Chicago milk epidemic which had been similarly utilized by Davis.[49] And it is again noteworthy that in less than one third of the affected joints were organisms recovered from the exudates.

The most recent studies that have attracted attention in connection with rheumatism are those of Small[43] and of Birkhaug.[44] Small worked with a strain of non-hemolytic streptococcus of the Gamma type isolated from the heart's blood of a patient who suffered from a typical attack of acute arthritis three weeks after the onset of a tonsillitis. The other thirty strains reported upon by Small were all obtained from throats, with the exception of two from the blood, three from the feces and one from extirpated tonsils. Again we wish to call attention to the fact that while Small obtained joint lesions in a number of rabbits, the cultures taken from these lesions by aspiration from the joints, whenever done, were negative. Birkhaug, whose streptococcus was isolated from the blood during life and from the mitral valve at autopsy, has developed the idea that the rheumatic joint lesions may be regarded as direct effects of a toxic substance produced by his strain, similar in general principles to the toxins obtained by the Dicks with the scarlatinal streptococci.

Of some interest in regard to the probability that no single organism is involved are two cases of acute rheumatic fever from which we obtained cultures recently and which will be reported later. In one of these a green-producing streptococcus was obtained from the myocardium at autopsy, and from the other a blood culture taken at the height of the fever showed two types of streptococci—one a typical Gamma strain like that described by Small, another one a typical viridans.

Whatever one may believe regarding the particular type of infectious organism responsible for acute rheumatic conditions, it seems reasonably clear that both in man and in animals in which acute joint inflammations have been studied the affected joints in the large majority of investigated cases are sterile to the ordinary cultural procedures. And again, neither the subsequent clinical course nor the pathological changes are indicative of localized acute pyogenic infection. If this premise is accepted, the problem concerning rheumatic arthritis is narrowed down to two lines of reasoning. Either the joint conditions are the results of the direct invasion of the joints by an organism still unknown, which has hitherto defied all cultural methods—perhaps a filterable virus, as Swift suggests in one of his papers; or the joint lesions represent remote effects of toxic influences referable to the presence of infecting organisms in other parts of the body. The first suggestion is nothing more than a vague guess resting upon no available evidence. Moreover, it eliminates all reference to the not inconsiderable evidence of the association of streptococci with the rheumatic symptom-complex in man and in animal experiments. The second possibility leaves us two alternatives to explain joint involvement—either a toxic effect due to direct entrance into the joints of a bacterial poison, or the allergic reaction following contact of a bacterial antigen with the joint tissues of a body specifically sensitive to this microörganism. In both of these mechanisms it would be necessary to assume an establishment of free communication between the circulating blood and the joint cavity by conditions of temporary capillary permeability, and this in rheumatism may often be furnished by chilling, exposure to wet and other accidents with which clinical experience has long associated the onset of a rheumatic attack. Either one of these alternatives would be in harmony with the increasing evidence of streptococcus association with rheumatism, and would be consistent both with the usual sterility of joint fluids and with the frequent absence of microörganisms

from the blood stream. Neither of them, in our opinion, would exclude direct bacterial causation of other manifestations of the disease, such as valvular vegetations, Aschoff bodies, etc.—these explanations being limited for the time being entirely to the conditions of the joints.

Causation by a specific toxin would, it appears to us, necessitate assumption of a single speific organism, which is inconsistent with the variety of streptococci that have been isolated and which is unnecessary if we regard allergy as the underlying mechanism. And, moreover, we believe that most of the observations recorded by Birkhaug could be explained by an allergic as well as by a toxin mechanism—perhaps more logically in view of the extraordinary heat stability of his "toxins."

The first experimental worker who clearly introduced the conception of sensitization into the problem of rheumatism was probably Herry.[42] Herry introduced extracts of his organisms into joints and sensitized the joints to subsequent lodgment of the bacteria intravenously injected. Faber,[50] following more or less along the lines of Herry and his predecessors, injected the joints with dead bacteria, using chiefly the *Streptococcus viridans,* and at various periods after the inflammation had completely subsided reinjected intravenously with the same cultures. He often obtained lesions in the sensitized joints of rabbits so treated, but it is apparent from the frequency with which he obtained positive cultures from the joint fluid, that he produced actual infections. Faber's work, therefore, while of considerable importance indicated only that a preceding inflammation created a locus of less resistance in which intravenously injected organisms could later find lodgment. It is true, indeed, that he claimed specificity in the sensitization, a point in which, however, his work is not convincing. Some years later, in 1923, Swift and Boots[47] took up the same question, carefully controlling fluctuations of virulence of the organisms used, and varying dosage and time relations, and came to the conclusion that specific joint sensitization did not render the joints so

treated more liable to inflammation than were other untreated joints of the same animals.

Our own interest in the allergic explanation of certain forms of rheumatic arthritis was stimulated by the publication of Faber.[50] Since Faber, however, was working on the idea of producing focal infections, our conception was rather more definitely encouraged by our interest in serum sickness. There is perhaps no more striking and definite example of the relationship of joint manifestations without actual joint infection than the frequent arthritic symptoms which follow in the case of therapeutic horse serum injections into man. And of similar suggestive significance is the fact that such joint manifestations are frequently influenced by salicylates and may move about from joint to joint in more or less the same manner in which acute articular rheumatism is apt to do this. With a pupil, Dr. Wu, we attempted some years ago to induce joint lesions in rabbits by injecting with horse serum until they possessed a high precipitin titer, then injecting the antigen directly into the joints themselves. Curiously enough, we never produced joint swelling in any of these rabbits on first administration, however highly the animals may have been immunized, but on second, third or fourth injection into the same joint definite signs of local sensitization were apparent. These experiments were abandoned at the time, with the hope that other methods of attack might prove more successful. We believe now that they were significant in showing that local sensitization is possible but that it requires, in addition to the immunological mechanism, some factor which establishes a free communication between circulating antigen or antibody and the joint cavity.

Subsequent studies were based largely upon our interest in bacterial allergy, and when a few years ago Grinnell and the writer succeeded in producing severe allergic reactions in guinea-pigs with streptococcus and pneumococcus substances, the matter was taken up again. So far, our chief studies that have reached anything like comple-

tion were carried out with guinea-pigs sensitized to pneumococcus autolysate. In a considerable number of these, when satisfactory skin sensitization had been obtained, injections into the knee joints were practiced—on one side with autolysate, on the other with salt solution—similar injections being made on normal animals at the same time. The results of these experiments may be summarized briefly by the table on the following page.

These nine guinea-pigs showing severely swollen joints were selected from a series of twenty-four. Six of the others showed moderate skin reactions and moderately swollen joints, and nine showed negative skin reactions and negative joints. In no case was the skin reaction positive with a negative joint, and in only one was the skin reaction severe and the joint only moderately swollen.

It is necessary to add again that our experiments, while showing marked parallelism between general hypersensitiveness and the reactions in the joints, were entirely unsuccessful in a number of experiments in which we endeavored to simulate the human conditions by reinjecting the sensitized animals intravenously or intraperitoneally, at the same time injuring the joints either by freezing with ethyl chloride, by puncturing with a sterile needle, or by injecting with salt solution. On the other hand, we not infrequently obtained joint lesions on first injection into the joint, never obtaining such lesions on similar injection into normal animals. Similar observations have recently been made in our experiments upon the sensitization of rabbits to streptococci in which the material used for skin and joint injection was a filtrate made by the technique of the Dicks. These experiments are being continued not only with hemolytic streptococci but with a streptococcus recently isolated from the myocardium of a child which died in the course of acute rheumatic fever. The pathological studies begun on such joints are not yet sufficiently advanced to be recorded. Our present work

Guinea-Pigs Injected into Knee Joint with Sterile Autolyzed Pneumococci

Increase of Reaction	Guinea-Pig	First Injection		Second Injection		Third Injection		Fourth Injection	
		Skin	Joint	Skin	Joint	Skin	Joint	Skin	Joint
	1.	Negative	Negative	Moderate	Severe				
	2.	Moderate	Slight	Slight	Severe	Slight	Severe		
	3.	Mild	Mild	Moderate	Severe	Diffuse Edema	Severe		
	4.	Mild	Mild	Slight	Slight				
	5.	Mild	Mild	Slight	Moderate	Slight	Severe	Moderate	Very Severe
Severe on	6.	Strong	Severe						
First Joint	7.	Mild	Severe	Moderate	Severe				
Injection	8.	Moderate	Severe	Moderate	Severe				
Decrease	9.	Moderate	Severe	Slight	Slight				

is being carried out along these lines with streptococci and streptococcus substances in the hope that the still missing links in the chain of reasoning may be forged.

We are quite aware of the fact that, up to the present time, we have added relatively little to the general evidence in favor of the allergic causation of rheumatic arthritis. But it is a difficult problem and, in our own case, has necessitated prolonged preliminary studies on bacterial allergy. It seemed to us, however, that in dealing with the influence of the allergic phenomena on infectious disease in general no phase deserved so complete discussion as this one, and that in no disease has so much indirect evidence been adduced for such a point of view by workers who had other objectives in mind. Summarizing it, we believe the allergic views of this malady logical for the following reasons:

(1) A definitely anaphylactic condition—serum sickness—is accompanied by joint symptoms showing many analogies to articular rheumatism.

(2) In acute articular rheumatism the joint fluids are usually sterile.

(3) In animals following bacterial injection that develop joint lesions the same is true.

(4) Experimentally it appears that the sensitiveness of joints can be demonstrated as to some extent parallel to general sensitiveness.

It would seem to us, also, that the allergic explanation is consistent with the variety of organisms that have been isolated and with the frequency with which exposure, etc., are associated with onsets of rheumatism in establishing abnormal circulatory conditions that lead to a freer communication between the circulation and the joints.

We are not by any means willing to assume that all cases of acute joint inflammation necessarily represent one and the same disease. We believe, however, that for the reasons stated above the allergeric explanation is a logical one for at least a considerable proportion of such

cases and more consistent with clinical and experimental facts than any other available explanation at the present time.

Summary and Conclusions

Bacterial allergy is a condition in which the body is sensitized to a bacterial antigen. We believe that this antigen, in its most potent form, results from biological disintegration of the bacteria, either by autolysis or a similar disintegration which takes place in inflammatory foci; and it is likely that many of the experimental difficulties that have been encountered are due to the diminution of functional properties coincident to chemical manipulation *in vitro*.

The allergic state represents an increased capacity on the part of the tissues to react to this antigen, which may either come to the body in the form of a new infection, or through the lighting up of an old focus. This increased capacity to react may be injurious and result in pathological changes and disease. On the other hand, in its deeper pathological significance it probably means merely that the tissues through specific sensitization are on a hair-trigger and can respond both cellularly and humorally to this antigen with a speed and vigor not possessed by the normal body. In this sense, the allergic state may in certain instances be regarded as an index of resistance—a thing which we believe to be true in the case of tuberculosis; and since the allergic state can be brought about by dead tubercle bacilli, we believe that attempts at active immunization in tuberculosis are at least as logical as immunization with attenuated living cultures, and manifestly safer.

It is probable that in order to produce any sort of noticeably acute pathological change in the tissues of a sensitive animal it is necessary that the antigen shall reach the tissues in a relatively concentrated state. This seems indicated by our own experience in obtaining violent hemorrhagic skin reactions with pneumococcus autolysate in

guinea-pigs which reacted hardly at all when the same and larger amounts of antigen were distributed over the entire peritoneum by intraperitoneal injection. It may also be that the situation is complicated by local differences in degrees of sensitiveness of individual tissues—a view which experiments in rheumatism encourage.

Finally, it seems to us that the work of the Dicks, of Dochez and, to some extent the experience of Grinnell and the writer, indicate that a new form of bacterial substance was discovered when the Dick toxin was brought forward. It seems that in this material we possess a heat stable bacterial product which is both a sensitizing antigen and can be neutralized by a serum. In the case of tuberculin no neutralization by immune serum has been possible, but with the streptococcus products both the Dicks and Dochez in their scarlet fever work, and Dochez in purposeful animal experiments on the study of allergy have shown that serum can be produced which will neutralize the allergic antigen; and his experiments with Stevens, as well as our own with Grinnell, have shown that animals can in the course of treatment pass through an allergic state into one of immunity to the same agent. And with this recognition a new type of immunological manifestation is being uncovered.

REFERENCES

1 Koch. *Deutsche Med. Wchnschr.*, 1891, xvii: 101.

2 Avery and Heidelberger. *J. Exper. Med.*, 1925, xlii: 367. (See this paper for other references, same authors.)

3 Zinsser and Mueller. *J. Exper. Med.*, 1925, xli: 159; Zinsser and Tamiya: *ibid.*, 1925, xlii: 311; Mueller. *Proc. Soc. Exper. Biol. & Med.*, 1924, xxii: 209.

4 Gay. *Am. J. M. Sci.*, 1915, cxlix: 157.

5 Baldwin. *Studies from the Saranac Laboratory for the Study of Tuberculosis*, 1904-1910.

6 Prudden and Hodenpyl. *New York M. J.*, 1891, lii: 637 and 697.

7 Zinsser and Petroff. *J. Immunol.*, March 1924, ix: 85.

8 Bail. *Ztschr. f. Immunitätsforsch., Orig.*, 1909, iii: 371.

9 Lange. *J. Med. Res.*, 1924, xliv: 293.

[10] Zinsser. *J. Exper. Med.*, 1921, xxxiv: 495.
[11] Atkin. *Brit. J. Exper. Path.*, 1926, vii: 167.
[12] Manwaring and Bronfenbrenner. *J. Exper. Med.*, 1913, xviii: 601.
[13] McJunkin. *J. Exper. Med.*, 1921, xxxiii: 751.
[14] Long. *Arch. Path. & Lab. Med.*, 1926, i: 918.
[15] Lowenstein. Kolle u. Wassermann Handbuch, 2. ed., 1913, v, 692.
[16] Calmette. *La Vaccination Preventive contre la Tuberculose par le B.C.G.*, 1927, Paris, Masson et Cie.
[17] Zinsser, Ward and Jennings. *J. Immunol.*, August, 1925, x: 719.
[18] Petroff and Stewart. *J. Immunol.*, 1926, xii: 97.
[19] Boecker and Nakayama. *Ztschr. f. Hyg.*, 1923, ci: 11.
[20] Nasta and Ionesco. *Comptes rend. Soc. de biol.*, 1924, xci: 506.
[21] Langer. *Klin. Wchnschr.*, 1924, iii: 1944.
[22] Fedders. *Deutsche Med. Wchnschr.*, 1925, li: 1659.
[23] Petroff. *Proc. Soc. Exper. Biol. & Med.*, 1927, xxv: 14.
[24] Dochez and Sherman. *Proc. Soc. Exper. Biol. & Med.*, 1924-5, xxii: 282.
[25] Zinsser and Grinnell. *J. Immunol.*, 1925, x: 725.
[26] Duval and Hubbard. *Exper. Med.*, 1927, xlvi: 379.
[27] Dochez and Stevens. *J. Exper. Med.*, 1927, xlvi: 487.
[28] Bristol. *Am. J. M. Sc.*, 1926, clxvi: 853.
[29] Cooke. *Proc. Soc. Exper. Biol. & Med.*, 1927, xxiv: 314.
[30] Mackie. *Brit. J. Exper. Path.*, 1927, viii: 129.
[31] Smith, J. *J. Path. & Bacteriol.*, 1927, xxx: 651.
[32] Ratner, Jackson and Gruehl. *Am. J. Dis. Child.*, 1927, xxxiv: 23.
[33] Walker. *J. Med. Res.*, 1917, n.s. xxx: 487; also, *J. A. M. A.*, 1920, lxxv: 782.
[34] Frank and Strauss. *J. A. M. A.*, 1919, lxxii: 1593.
[35] Koessler and Moody. *J. A. M. A.*, 1915, lxiv: 1104.
[36] Duke. *Asthma, Hay Fever, etc.*, St. Louis, C. V. Mosby Co., 1925: 131.
[37] Foster. *J. Infect. Dis.*, 1917, xxi: 451.
[38] Kruse. *München Med. Wchnschr.*, 1914, lxi: 1547.
[39] Levaditi, Nicolau and Harvier. *Comptes rend. Soc. de biol.*, 1921, lxxxv: 195.
[40] Swift and Kinsella. *Arch. Int. Med.*, 1917, xvii: 381.
[41] Swift. *Nelson's Loose Leaf Medicine*, 1920, i: 401.
[42] Herry. *Bull. Acad. roy. méd. Belgique*, 1914, ser. 4, xxviii: 76 (cited from Faber).
[43] Small. *Am. J. M. Sc.*, 1927, clxiii: 101.
[44] Birkhaug. *J. Infect. Dis.*, 1927, xl: 549.
[45] Smith and Brown. *J. Med. Res.*, 1914, xxxi: 455; and *Monographs Rockefeller Inst.*, 1919, ix.
[46] Rosenow. *J. A. M. A.*, 1913, lx: 1223.
[47] Swift and Boots. *J. Exper. Med.*, 1923, xxxvii: 553.
[48] Rothschild and Thalheimer. *J. Exper. Med.*, 1914, xix: 429 and 444.
[49] Davis. *J. A. M. A.*, 1912, lviii: 1283; Davis and Rosenow. *ibid.*, 773.
[50] Faber. *J. Exper. Med.*, 1915, xxii: 615.

*LOBAR PNEUMONIA CONSIDERED AS A PNEUMOCOCCIC MASSIVE ATELECTASIS OF THE LUNG

(ABSTRACT)

POL. N. CORYLLOS and GEORGE L. BIRNBAUM

During our experimental work [1] on massive atelectasis of the lung, we observed such striking similarities between massive atelectasis and lobar pneumonia that we were stimulated to investigate this problem further and to present our findings. Our work is far from being terminated; but the importance of positive results obtained so far seems so great that we are presenting this preliminary report with the hope and belief that it may be of some help to other investigators on lobar pneumonia.

We came to the conclusion that lobar pneumonia must be considered as a "pneumococcic massive atelectasis of the lung" and bronchopneumonia as an infectious patchy or lobular atelectasis; that a pneumococcic infection of the bronchial tree is not sufficient to produce lobar pneumonia. Another factor is necessary for determining this lobar pneumococcic cellulitis of the lung and this is: The occlusion of a bronchus exactly as in massive atelectasis, the obstruction being due to the particularly tenacious fibrinous bronchial pneumococcic exudate and to the inflammatory edema of the bronchi. If our interpretation of the experimental facts be accurate and the theory based upon them right, a number of features in pneumonia inexplicable to this date can receive a simple and easy explanation; these are: Its lobar distribution, the sudden onset, the crisis, the abortive forms, the predominance of localization in the inferior lobes, the often found displacement of the heart and diaphragm to the affected side, etc.

Furthermore from the similarities between lobar pneumonia and massive atelectasis, both being to our mind

*From the Department of Surgical Research, Cornell University Medical College, New York City.

secondary to bronchial occlusion, may arise the possibility of an additional mode of treatment, perhaps more surgical than medical, at least in the earliest period of pneumonia. In this preliminary report we shall give the results of our experimental work, with the hope that shortly we shall be able to report clinical results; and a brief resumé of the bronchoscopic examination, and bronchial aspiration of a human pneumonia case. This latter corroborated our experimental findings.

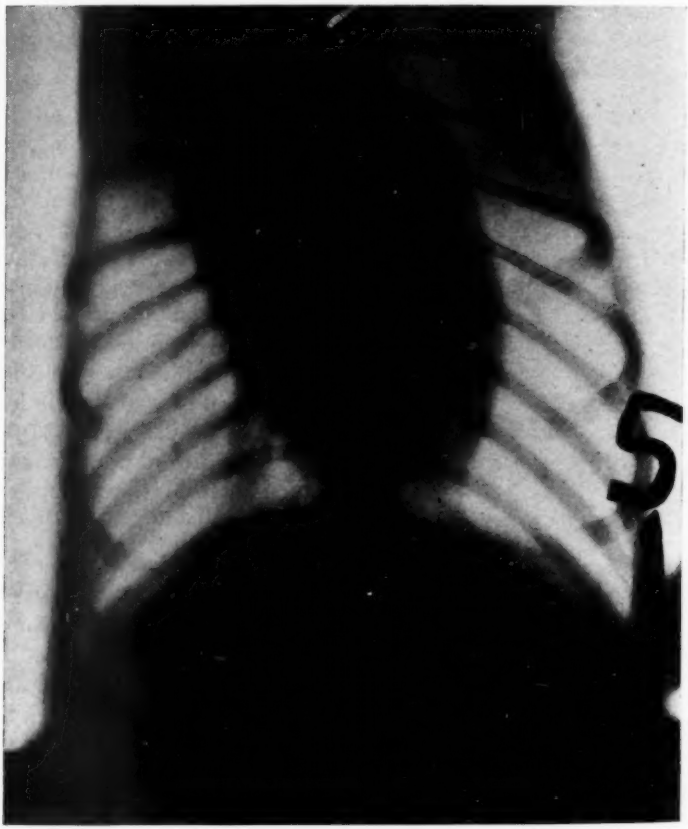
Massive atelectasis of the lung is characterized clinically by its dramatic onset with pain, dyspnea, often cynanosis, elevation of temperature and acceleration of pulse, dullness of one or several lobes with displacement of the mediastinum and its contents, trachea and heart, to the affected side and elevation of the diaphragm of the same side. Rarely cataclysmic and fatal, massive atelectasis usually ends after a few days by crisis, or lysis. In our investigation of the etiology and mechanism of postoperative atelectasis we came to the conclusion that the exciting cause is only one—the occlusion of a bronchus by mucous secretion; the other causes advanced, such as pain, narcotics, posture, limitation of respiration and cough, inhibition reflexes and disturbances of the ciliary epithelium being only predisposing factors.

In a previous work [2] we perfected a new technique consisting in the use of a small elastic balloon in which was incorporated a one-way valve by means of which the balloon could be filled with concentrated solution of sodium bromid, opaque to the X-ray, and thus made visible on the plate. By this procedure we have been able to block a given bronchus. After blocking the bronchus the clinical and X-ray evolution was typical of massive atelectasis.

All of our X-rays are strictly symmetric pictures taken with a special apparatus for avoiding distortion so far as possible. To avoid the irritating effect of narcotics on the respiratory tract the anesthetic used was isoamyl ethyl barbituric acid (amytal) injected into the peritoneum.

We give here only two of our 53 experimental cases on massive atelectasis to which our pneumonia cases will have to be compared later.

FIGURE 1



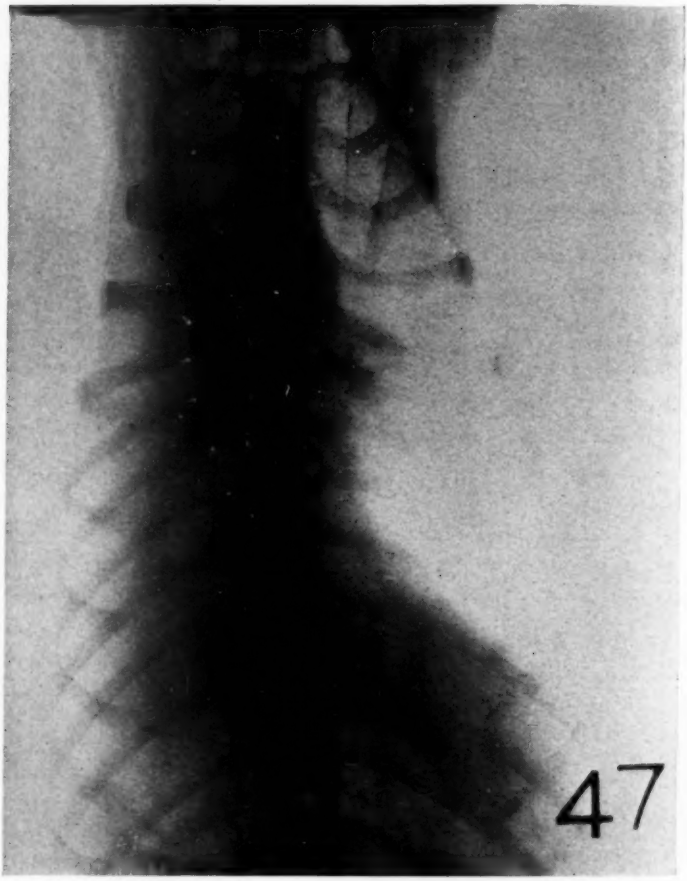
In dog 251 (fig. 1), the left bronchus was blocked. After twenty-four hours a complete left collapse was produced (fig. 2). Notice

FIGURE 2

the clear triangular area marked by letter "T," which is due to encroachment of the good lung upon the affected side and presents a curious similarity to the sonorous triangle described by Lord [2] in pneumonia.

In dog 47, the right main bronchus was occluded. Twenty-four hours later it presented the classical clinical symptoms of atelectasis, the heart being completely to the right and the lung more cloudy

FIGURE 3



(fig. 3). The same phenomenon can be obtained at will on either side.

There are a strikingly great number of points in common between lobar pneumonia and massive atelectasis. The more important are:

(1) The lobar distribution.
(2) The rapid onset of symptoms.
(3) The almost identical clinical symptoms, except for the more toxic element in pneumonia.
(4) The very rapid improvement after release of the obstruction in atelectasis, and after the crisis in pneumonia.
(5) The more usual localization in the inferior lobes, particularly the right.
(6) The X-ray findings.
(7) The gross pathology and histology.

The problems we were confronted with at the beginning of our experimental investigation on pneumonia were chiefly two:

(1) Why is there in lobar pneumonia a lobar distribution exactly as in massive atelectasis?
(2) If lobar pneumonia be due to a similar mechanism, there should be at least at its onset signs of an atelectasis which must be revealed by X-ray.

In the literature we found no explanation for the lobar distribution of pneumonia, though several authors have conceived the necessity of another cause besides the presence of pneumococci in the bronchi for determining the development of lobar pneumonia as, for example,—the influence of cold, nervous reflex, etc. Other authors have noticed in autopsies on pneumonia the occlusion of large bronchi by tenacious mucus. Blake and Cecil [3] working on monkeys have shown that in pneumonia the lesions start at the hilar part of the lobe, and that when this portion presents red hepatization the smaller bronchi are still sound. Another fact of importance is that the most frequent agent of lobar pneumonia is the pneumococcus which

is precisely the greatest fibrin producer of the group of micro-organisms known to produce pneumonia. Furthermore, Chevalier Jackson and his associates have prevented or cured so-called diptheritic pneumonias by careful bronchoscopic aspiration of the membranes. All these facts taken together offered valuable *a priori* support to our surmise that lobar pneumonia possibly owes its localization to the obstruction by mucus or exudate of a bronchus supplying a lobe. We therefore tried to find out whether signs of atelectasis were present in experimentally produced pneumonias, figures of which are later shown.

It is generally known that a differential diagnosis between postoperative massive atelectasis and postoperative pneumonia may be very difficult. Thus some report atelectasis complicating pneumonia or the inverse, pneumonia complicating atelectasis. Very often in cases of obscure postoperative lung complication the consulting medical man states that the case is clinically a pneumonia, but not typically so, because of the lack of toxic symptoms. In other cases, from the case history alone, it is impossible to state whether the disease has been massive atelectasis or pneumonia. True lobar pneumonia may occur in children with unquestionable signs of atelectasis as in the cases of Thoenes, St. Engel, Wallgren and Griffith. Griffith [4] denies the presence of signs of atelectasis in his case. We, on the other hand, believe that shifting of the heart and mediastinum and elevation of the diaphragm signifies but one thing: Decrease in size of the affected lobe with compensatory distention of the good lung—in other words, massive atelectasis. In text-books of pathology, the affected lobe seems larger than normal; likewise in a photograph of a specimen of a right pneumonia of a monkey's lung (fig. 4). However, the true size relations are different as we have observed in experimental atelectasis and lobar pneumonia. The true relations in size may be obtained *by first clamping the trachea* before removing the lung from the chest, as in dog 28, which had a right lobar pneumonia (fig. 5).

FIGURE 4

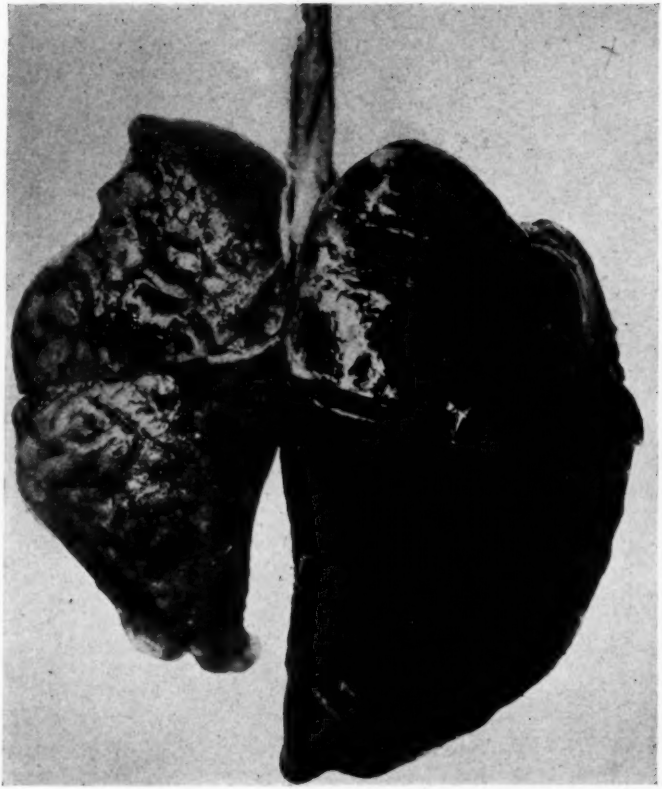


Fig. 4.—Right lobar pneumonia in monkey's lung (After Blake and Cecil).

FIGURE 5

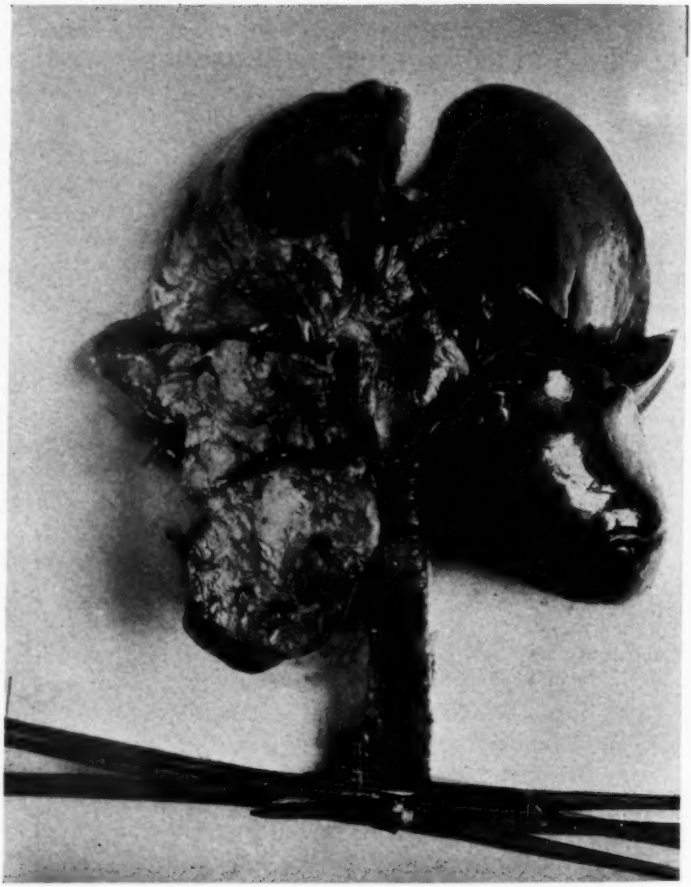


FIG. 5.—Right experimental lobar pneumonia in a dog's lung. The trachea has been clamped before opening the chest.

Even with the trachea clamped, the good lung decreases in size, because of diffusion of the alveolar air, and in a short while becomes even smaller than the affected lung. With no clamp, the good lung collapses immediately and an erroneous impression may be gotten.

Our experimental work has been carried out in dogs because of the flexibility of the mediastinum. With a Jackson bronchoscope, a nineteen to twenty-two hour old broth culture of pneumococcus type I, supplied by the Bellevue laboratory of Dr. Russell Cecil, was insufflated into the desired bronchus. Such culture in one to a million dilution in 1 c.c. amounts, killed white mice in twenty-four to seventy-two hours. The dogs were examined as to clinical signs, X-rays taken one, two or more times a day, blood counts and cultures taken every day, and post-mortem findings carefully noted. Using 10 c.c. amount of culture, we obtained negative results in about 20 per cent. which is proof that the volume of fluid alone is not sufficient to give an atelectasis.

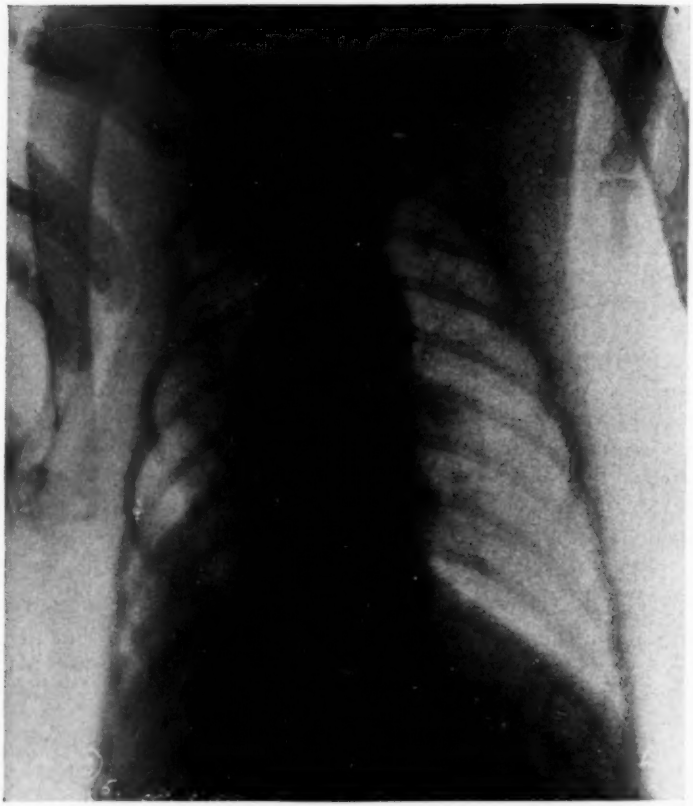
Dogs insufflated with 15 c.c. of culture of low toxicity did not develop pneumonia or atelectasis, showing that the volume of fluid alone insufflated is not the factor determining atelectasis.

Finally, a short summary of a human case of pneumonia is given. So far as we know, it is the first instance where bronchoscopy and bronchial aspiration has been done in pneumonia from the therapeutic point of view.

We shall simply state here, subject to further development in another paper, that the continuous raising of rusty sputum during the disease in humans is not in variance with our theory, because the sputum has its origin in the bronchi and major bronchioli and not in the alveolar air sacs, atria or small bronchioli.

Dr. Lewis A. Conner and Dr. J. D. Kernan kindly cooperated with us and procured the clinical data and the bronchoscopic examination of the patient.

FIGURE 6



Dog B5 had 10 c.c. of culture insufflated into right bronchus. Twenty-four hours later T. 104°, P. 160, R. 72; it was very sick and dyspneic. Blood count 13,850, blood culture positive for pneumococcus. X-ray shows heart displaced to the right, right diaphragm markedly elevated (fig. 6). Forty-eight hours later X-ray shows no change. The same day, fifty-two hours after insufflation, no change. Dog died four hours later. Autopsy: Pneumonia of all right lobes, so-called "stage of red hepatization." Microscopic section typically atelectatic with beginning exudate into alveoli.

FIGURE 7

Dog B27 had 1 c.c. of culture, representing the sediment of 12 c.c. of centrifuged culture, insufflated into its left main bronchus. Twenty-two hours later, complete pneumococcic atelectasis (fig. 7). Left bronchus aspirated, and 5 c.c. of viscid fluid removed. Animal died shortly after with positive blood culture and marked leukopenia, W.B.C. 2,400, polys 94 per cent. Lungs airless, bluish-red, stage of "red hepatization."

E. F. male, 23, was admitted Dec. 29th, 1927, 7 P. M. to the New York Hospital, on the medical service of Dr. Lewis A. Conner.

Relevant history: Two weeks before admission patient developed a slight "cold" characterized by mild rhinitis occasional cough which was slightly productive of mucoid sputum. On Dec. 27th, at 8 P. M., (forty-eight hours before admission) he suddenly developed a "shaking chill" lasting half an hour, followed by feverishness, malaise, bodily aches and increased cough. On Dec. 28th at 3:30 A. M. he vomited three times; later the same morning he coughed up blood-tinged sputum and "noticed a stitch in the left side on deep breathing." He then decided to enter the hospital.

Physical exam.: Patient appears acutely ill, face slightly flushed, respiration increased; coughs up a frothy orange colored sputum.

Chest: Heart normal, apex in 5th interspace 9 cm. to left of sternum.

Lungs: Right lung normal.

Left lung: Anteriorly the percussion note is resonant with suggestion of tympany. Posteriorly the note over the lower lobe is very dull. Over the dull area the fremitus is increased, with bronchophony and increased whispered voice. The breath sounds here are bronchial in character; occasional crepitant rales are heard. Sounds suppressed in axilla.

Rest of physical examination essentially negative.

On admission, T. 103.6°, P. 94, R. 30. Blood count 23,000 white cells, 97 per cent. polymorphnuclears. Sputum showed pneumococcus type III. X-ray at 8:40 P. M. on night of admission showed increased density throughout practically the entire lower left lobe; heart in mid-line, left diaphragm slightly higher than the right; trachea deviated slightly to the right. At 8 P. M. the same night bronchoscopy was done by Dr. J. D. Kernan. A 9 mm. bronchoscope was passed down the left bronchus with the

aid of cocain anesthesia. The first posterior root of the inferior bronchus was found to be occluded with thick tenacious rusty-colored exudate. No air was seen entering or leaving this bronchus, though an occasional bubble of air would come from the mass of viscid exudate. Approximately one teaspoonful of this material was aspirated. The other roots of the inferior bronchus, the bronchus of the other left lobe and the main bronchus were normal in appearance.

Progress Notes:

Dec. 30th (day following bronchoscopy): No untoward signs following bronchoscopy. Some signs of consolidation in left lower lobe anteriorly. T. 104°, P. 100, R. 25. General condition good. Blood culture negative.

Dec. 31st. Signs of consolidation present in left lower lobe. General condition good. T. 104°. X-ray shows no marked change.

Jan. 1, 1928. Temperature started to fall yesterday, forty-three hours after bronchoscopy, reaching normal within twelve hours. Crisis started within less than four days after onset of disease.

Jan 2nd. Blood count normal; advent of small moist rales in affected lobe.

Jan. 9th. Chest clear by physical and X-ray signs.

Jan. 13th. Discharged cured.

Summary

In a brief way, a resumé has been given of considerable data accumulated on experimental pneumonia in dogs. The similarities between lobar pneumonia and massive atelectasis have been pointed out. In our opinion the sequence of pneumonia is as follows: In the course of a pneumococcic infection of the bronchial tree, occlusion of a lobar bronchus occurs and this starts the syndrome called lobar pneumonia. This obstruction is effected by the viscid fibrinous bronchial exudate, aided perhaps by edema of the mucosa and possible damage to the ciliated

epithelium. We always found a brownish, viscid substance in the affected bronchi of our animals, which died of "lobar pneumonia." The lung was bluish-brown, airless, and section showed gradations from atelectasis to "red hepatization," as the latter appears in dogs.

In massive atelectasis the bronchus is often occluded by a relatively poorly infective secretion, and the toxic symptoms are absent; whereas in "lobar pneumonia," the viscid occluding secretion is infected with pneumococci from the start, the number and virulence of the microbes determining the degree of toxicity of the disease. The obstruction having once set in, absorption of alveolar air proceeds; simultaneously the infection is spreading to the periphery of the lobe by the septal and interalveolar lymphatics. Absorption of endotoxins in pneumonia explains the toxic element which is usually absent in simple atelectasis, but which can occur in the latter, if it is secondarily infected with pneumococcus, in which case we will have a postoperative pneumonia.

Conclusions

From the experimental and clinical facts, we have come to the following conclusions:

(1) Pneumonia in dogs presents the same X-ray signs and pathological findings as massive atelectasis.

(2) The two diseases are similar in their main clinical features. They differ in their degree of toxicity.

(3) Microbes are always more or less present in the obstructing bronchial secretion, in simple atelectasis. When virulence of these microbes is high, the toxicity of atelectasis approaches or even surpasses that of pneumonia. When the infecting agent is pneumococcus the disease then becomes identical with so-called "lobar pneumonia," and no differentiation is possible.

(4) Lobar pneumonia is a pneumococcic massive atelectasis of the lung.

(5) Bronchoscopic liberation of the occluded bronchus has already given conclusive results in massive atelectasis and even in postdiptheritic pneumonia. If we are right in the interpretation of the experimental and clinical facts presented, bronchoscopic aspiration in pneumonia, at least in the earliest stages of this disease, would be indicated. It is too early as yet to give definite conclusions concerning such therapy, but its employment, at least in early cases of lobar pneumonia, should merit the consideration of the clinician.

(6) A human case has been bronchoscoped and the findings corroborated our experimental observations. The bronchus corresponding to the affected lobe, and only this bronchus, was occluded by mucous exudate.

BIBLIOGRAPHY

[1] Coryllos, P. N. and Birnbaum, G. L. Obstructive Massive Atelectasis of the Lung. *Arch. Surg.*, Feb., 1928, xvi: 501.

[2] Lord, F. F. *Diseases of the Bronchi, Lungs and Pleura.* Phila., Lea & Feibiger, 1915.

[3] Blake, F. G. & Cecil, R L. *J. Exper. Med.*, Apr., 1920, xxx: 445.

[4] Griffith, J. P. C. *Am. J. Med. Sc.*, Oct., 1927, clxxiv:448.

We wish to express our great appreciation to Drs. Russell Cecil, John C. Torrey and Morton Kahn, for their kind suggestions and help, and to Miss Dorothy Rhoades and Miss Elizabeth Montu of their laboratories for their kind coöperation.

ABSTRACTS OF PAPERS DELIVERED AT SECTION MEETINGS

Section of Pediatrics, January 12, 1928

ENDOCRINE GLANDS IN RELATION TO INFANCY AND CHILDHOOD

(ABSTRACT)

LEWELLYS F. BARKER

Baltimore

The topic is of interest to pediatrists: (1) Since some of the disease-syndromes of infancy and childhood are due to excess or deficiency of products of the endocrine glands, (2) since the metabolic processes and the activities of the vegetative nervous system are subject to endocrine regulation, (3) since early development, both mental and physical, are influenced by the increta and (4) because human constitutions appear to differ markedly in endocrine make-up. But it should be emphasized that though the facts in endocrine domains are interesting, the fancies that are prevalent are almost too fascinating. Real progress is being made in endocrinology; even its errors through stimulating further researchs are leading to the discovery of new truths.

Of the clinical syndromes of probable endocrine origin interesting to pediatrists, the more important are (1) Graves' syndrome or hyperthyroidism, (2) hypothyroidism, (3) tetany (manifest and latent, (4) gigantism, (5) dystrophia adiposogenitalis, (6) diabetes insipidus, (7) status thymicolymphaticus, (8) hypoadrenia (9) pseudohermaphrodism, (10) premature puberty, (11) eunuchoidism, and (12) diabetes mellitus. The paper dealt with the more important features of these syndromes in the early ages of life.

Comment was made upon the use of autacoid substances as pharmaka, and the uses in the therapy of childhood

diseases for thyroxin, epinephrin, pituitrin, insulin, and parathormone were briefly described. A warning against the abuse of these new remedies was sounded, since they are powerful agents capable of producing dangerous reactions unless most cautiously administered.

The relations of endocrine studies to the newer concepts of the psycho-physical constitution were next considered. Though neural and hormonal influences are important in the integration of developing constitutions, it should not be forgotten that the nervous system and the incretory system are, themselves, genotypically determined, even though they may be to some extent modified by paratypic influences as phenotype succeeds phenotype in the development of single persons. The importance of fostering the studies now being undertaken in so-called " constitution clinics" was pointed out; only after these and other researches have been pushed much farther can we hope to give any specific meaning to what is sometimes referred to as the "endocrine formula" of a human constitution! Attention, too, should be focussed upon the very important studies upon the effects of very early injuries to developing organisms upon their subsequent history.

February 9, 1928

THE KETOGENIC DIET IN EPILEPSY

Fritz B. Talbot

Boston

Until further investigation has provided us with an absolute standard, somewhat arbitrary criteria must serve as indications of the effectiveness of treatment in epilepsy. To permit satisfactory comparison of different studies, the same criteria should be used by all investigators. I shall therefore in this discussion employ the standards used by Helmholz for "complete relief," "improvement," and "failure."

The ketogenic diet, of which Wilder first conceived, has been used during the last six years in several clinics in the treatment of epilepsy. Although none of its advocates have claimed that it cures the basic abnormality, those who recommend the diet realize that it may in some way affect the underlying cause of epilepsy. This is suggested by the permanence of the relief which seems to follow a course of treatment in some cases. The results of ketogenic therapy in different hospital clinics are surprisingly uniform. Epileptic seizures disappear completely in about 33 per cent. of all children treated. The proportion of adults who are thus entirely relieved is smaller, for mature individuals seem to respond less readily than children. A few do, however, find that strict adherence to the diet brings complete relief and a large number have much less severe symptoms during the ketogenic regime.

That the effectiveness of the treatment probably depends in part at least on the nicety with which the diet is adjusted is suggested by the few data compiled in Table I. The percentage of complete relief in the children in the Research Ward of the Massachusetts General Hospital is just twice that found in the usual clinic. The results obtained in the Children's Ward are similar to those published by Peterman and Helmholz, and those seen in private practice are somewhat more encouraging. The discrepancy in the percentages cannot be ascribed to great differences in the methods employed, for in all groups the same principles of therapy were followed. In private practice, and particularly in the Research Ward of the hospital, however, more detailed attention and care can be given than is possible in a large clinic.

Just how and why the ketogenic diet exerts its beneficial effect is not known in spite of careful investigation of many of the metabolic changes induced. The improvement in symptoms which accompanies both fasting and administration of this special diet is associated with acidosis, ketosis, lowering of the sugar content of the blood, and a diminution of the alkaline reserve. Each one of these factors has

been separately studied with the hope of finding an explanation for the effectiveness of the treatment, but without avail. Mineral acidosis induced by the administration of ammonium chloride does not exert the desired effect; slight lowering of the blood-sugar-content by means of insulin is not followed by definite improvement, and administration of sufficient doses to reduce the content to 40 mg. per 100 c.c. brings on almost continuous convulsions which are relieved by glucose;* administration of bicarbonate of soda does not induce attacks in our patients as it would if a shift of the acid-base equilibrium toward the alkaline side were the critical factor. With these possibilities ruled out, we are still completely in the dark as to whether there is any etiological connection between epileptic seizures and metabolism.

Wilder's hypothesis, that the anesthetic action of acetone may be responsible for the improvement which follows ketogenic therapy, still remains and deserves consideration. Parsons in his experiments in the Children's Clinic at the Massachusetts General Hospital has confirmed the long-recognized fact that this substance has depressing properties similar to those of ether. In his rabbits acetone caused unconsciousness, complete anesthesia, and, in large doses, death. These symptoms disappeared completely on intravenous injection of 10 per cent. glucose solution and death was averted by the same means. Although this anesthetic action of acetone explains more satisfactorily than any other factor the results obtained, it does not throw light on the greater sensitiveness of certain individuals to given degrees of ketosis and on the discrepancy between the response of adults and that of children to dietary treatment. Neither does it suggest a reason for the apparently complete and permanent relief of symptoms in certain children even after the return to a non-ketogenic diet, and the reappearance of symptoms in other children before ketosis has completely disappeared.

*Metcalf, Kenneth M., and Moriarty, Margaret E.: Unpublished data from Children's Medical Clinic, Massachusetts General Hospital, Boston.

Before discussing in detail the essential constituents and the administration of the ketogenic diet, it may be well to point out some of the general non-specific effects of this type of treatment when it is properly adapted to the individual. Maintenance of marked ketosis for months does not seem to injure the general health, and in most epileptic patients is accompanied by constitutional improvement. The susceptibility to current infections appears to be reduced, and the resistance to all types of sickness seems to be greater. Children continue to gain weight normally and are not stunted in their growth. In other words, maintenance of an apparently abnormal diet in epilepsy just as in diabetes establishes a condition of general well-being.

The preparation and administration of the ketogenic diet requires special knowledge just as does the use of the diabetic diet. It is not sufficient to tell the patient to eat a lot of fat and to omit carbohydrate food. Specific directions must be given about the weight of each article of food, and punctilious watchfulness must be maintained to ascertain that without exception the patient receives the exact quantity prescribed and nothing else. Small aberrations retard improvement disproportionately. Since physiological adaptation to change of any sort cannot take place instantly, the shift from a normal to a ketogenic diet should be gradual. The intake of ketogenic substances should increase as the intake of antiketogenic material is reduced. Because the mathematics involved in Schaeffer's molecular ratios is so complicated, and because in actual practice molecular ratios do not differ markedly from gram-ratios, the ketogenic-antiketogenic proportions of the diets used in the clinic at the Massachusetts General Hospital and in my private practice are calculated on a basis of weight. Protein and carbohydrate are considered antiketogenic and fat ketogenic. Since the ketogenic-antiketogenic ratio of the usual normal diet is 1:4 and the best therapeutic results in epilepsy are not obtained until the ratio has approached 4:1, there must be several stages between the beginning of treatment and the establishment

of a fully effective regime. The digestion requires time for its adjustment to the lack of carbohydrate and protein and the presence of large quantities of fat. Too rapid change results in abdominal discomfort, nausea and other symptoms of indigestion. These disturbances usually yield in a short while to simple therapeutic measures without any shift of diet, but it is preferable, of course, to make the change to the ketogenic regime without inducing such upsets.

The technic used with the patients here discussed is identical in principle with that of Peterman and Helmholz, but differs from it in detail. No period of complete fasting precedes the alteration in the food intake, but the shift from one type of diet to the other is made gradually. Luther's working table (Table II) is of great value during this period of adjustment, for it permits easy calculation of the ketogenic-antiketogenic ratio of any diet containing 1000 to 2500 calories. It is usually best to change the proportions of the diet from normal to 1½:1, and thereafter to follow the sequence of 2:1, 2½:1, 3:1, 3½:1, 4:1. Occasionally, some of the stages can be omitted when it is essential to induce ketosis quickly or when the patient has a very strong digestion. The response to the diet varies greatly in different individuals, and can be determined by chemical tests. Early ketosis is revealed by the presence of acetone in the breath (Higgins' method) and may appear while the ratio of the food constituents is 1½:1. The sodium nitroprusside test in the urine does not become positive until the ratio of the diet is 2:1; and the ferric chloride test remains negative until the proportions reach 2½:1.

In planning the ketogenic diet it is essential to consider the caloric content of the food, the protein needs of the individual, and probably the effect of ketosis on the mineral metabolism of the body. The number of calories should be such that the ideal weight may be maintained and growth may continue normally in children. If the proper adjustment has been made underweight children will at

first gain rapidly in weight, and obese children will lose. Weekly determination of the weight demonstrates clearly whether these qualifications are being fulfilled. The average child needs about 50 per cent. more than the calculated basal caloric requirement for an individual of the same height and age, but variations in activity make it impossible to determine the correct intake without careful checking. Table III gives the average caloric requirements, and has in our studies proved to be a satisfactory working basis. It cannot be followed blindly, however, for a patient whose physical development is above the average requires more calories than one who corresponds exactly with the standards. The caloric intake must be adjusted to the developmental age and to the activity of the individual. That of physically active children must be more nearly maximal than that of children who take but little exercise (Chart I). Many observers, however, prefer Peterman's method of calculating the requisite number of calories. He gives a diet containing 30 calories per pound of body weight.

Concerning the protein needs of the body there has been much speculation. Recent investigations have suggested that small amounts of protein in the food suffice for growth and ordinary wear and tear, but the requirements have not yet been accurately determined. It is well recognized, however, that an effective ketogenic diet (ratio 4:1) contains so little protein that there is danger of failing to supply the minimal demand. Bartlett's work on diabetic children seems to indicate that 1 gram of protein per kilo of body weight is sufficient. Peterman administers this quantity to children less than five years of age, and 2/3 of a gram per kilo to those who are older. The technic at the Massachusetts General Hospital has been to give about 1 gram per kilo to children of all ages. This appears to be sufficient before the ketosis is marked, provided the total food intake is adequate. Thereafter the nitrogen balance may become negative (Chart II, Tables IV and V).

Just how long and to what degree fat can replace carbohydrate in the metabolic processes is not known. It does supply calories and to some extent prevents inroads on the body protein, but it is very improbable that it can duplicate in full the protein-sparing action of carbohydrate. In order to discover the effect of a high-fat-low-carbohydrate diet on the retention of protein the intake and output of some of our patients has been determined. The data obtained show that during ketosis a positive protein balance is not maintained in children more than eight or ten years old until the intake is about 1¼ grams per kilo of *expected body weight*. This suggests that in the long run the amount of protein in the diet should be larger than has previously been thought necessary. No available evidence indicates the damage done to the body by persistence of a negative nitrogen balance, but it is reasonable to suppose that an indefinite quantity of protein cannot be lost without real injury of some sort. Consequently it is very desirable to determine the balance from time to time during dietary therapy, and almost essential to do so when the diet is extreme in any way. This can be done in private practice as well as in hospital clinics. We have made it a routine procedure to analyze the urine quantitatively for nitrogen at intervals during treatment, and on the basis of the results obtained to vary the diet so that the balance is positive. Daily examination has, however, demonstrated that the excretion varies greatly from day to day even when the intake is constant, and that single determinations have no significance (Table VI).

Certain factors other than the action of carbohydrate and fat seem to affect the retention and availability of nitrogen in the body. The physiological properties of animal and vegetable proteins are not identical, and gelatine and the substances which break down into the amino acids seem to act differently. The reason for this is not known.

The mineral requirements of man are comparatively little understood. Gamble's work shows that ketosis increases the calcium excretion, a fact which must not be

forgotten in the administration of the ketogenic diet. This is not disproved by the observation that the calcium-content of the blood remains stationary during ketogenic therapy, for Aub has found that the rate of calcium excretion may markedly increase while the blood content remains normal. Consequently until the conditions are exactly understood it seems reasonable to avoid the danger of decalcification of the skeleton by giving small doses of calcium lactate (2-3 grams daily) during prolonged ketosis. Inclusion of adequate quantities of calcium in the food is impossible when the fat ratio is very high, because sufficient amounts of milk would upset the proportions of the diet.

Summary

The effects of the ketogenic diet in children have been successful enough to warrant the use of this form of therapy. The diet should contain sufficient calories to maintain the weight, and sufficient protein to prevent loss from the body. The amount needed for this during ketosis is greater than has been generally assumed. The minimal requirements are probably met by 1¼ grams of protein per kilo during ketosis. Studies are now under way to establish the minimal calcium requirement during ketosis.

THE KETOGENIC DIET

M. G. Peterman

Milwaukee

The ketogenic diet was introduced in 1924 after two years of clinical trial. Wilder, in 1921, on the basis of Geyelin's results with starvation, suggested that diets in which the proportion of carbohydrate and protein were sufficiently restricted might offer a method of treatment of epilepsy. It was on the basis of Wilder's suggestion that the high fat, low carbohydrate, restricted protein diet

was evolved. Studies of patients on this diet and modifications of my original procedure have been reported by me during the past three years. Other investigators have reported results in the treatment of epilepsy with the ketogenic diet, but there have been no modifications of my procedure, nor have there appeared any other original explanations of the action of the diet in its control of epileptic seizures.

In the preliminary report it was suggested that the object of the diet was to produce acidosis. This object was based on the results reported in 1921 by Jarloev and by Geyelin. Geyelin was the first in this country to report the beneficial effects of fasting on epileptic patients, and he ascribed the results to an acidosis produced. Three years later Hoeffel and Moriarty, and Shaw and Moriarty subscribed to the acidosis theory of Jarloev and Geyelin. In 1925 and subsequently it was demonstrated that acidosis alone or ketosis alone do not control the convulsions of epilepsy. Children on the ketogenic diet may be given enough soda to alkalinize the urine without provoking attacks. The ketosis is variable during this procedure but usually persists while the acid-base equilibrium is shifted toward the alkaline. A chemical acidosis produced by the administration of ammonium chloride in large amounts does not control the convulsions of epilepsy. With this drug the CO_2 combining power of the blood may be reduced to 20 volumes per cent and the pH of the urine to 5.4. The fat in the diet may be substituted with "intarvin" until the acetone bodies disappear from the urine or are considerably diminished and still the patient be kept free of attacks. However the effect of pyruvic acid, the incomplete oxidation product of intarvin, is not known. Authors should be more careful to distinguish between acidosis and ketosis. It has been demonstrated that the ketogenic diet produces a ketosis in which the acetone bodies may be increased from two to forty times normal. This increase is evident in the blood, urine, alveolar air, and probably throughout the tissues. There is usually a slight fall in the alkali reserve or a decrease in the CO_2

combining power of the plasma but not below the limits of normal. Talbot and his co-workers in their report still favored our original acidosis theory but in their conclusions they agreed with our subsequent ideas on the predominant effect of the ketones. McQuarrie and Keith have recently subscribed to this proposal. They have also further substantiated our earlier demonstration that the degree of ketosis is a factor in the control of epileptic seizures. The fall in blood sugar is not always great or consistent. The normal variation of fasting blood sugars is well known. In ketosis the level is dependent on a number of factors including the storage of glycogen before ketosis; the degree of ketosis; the total caloric intake; individual susceptibilities; and rate of absorption. Brown and Graham, McQuarrie and Keith, and others find no consistent decrease. There is no change in the calcium, phosphorus, chlorides, or non-protein nitrogen of the blood. There is also no change in the number of blood cells or in the sedimentation reaction. The effects of the ketogenic diet as outlined above are not, as suggested by McQuarrie and Keith, "entirely similar to those of fasting." It has been sufficiently demonstrated that in ketosis the acetone bodies are increased in a much higher proportion and that they persist for longer periods. There is also not the marked decrease in the CO_2 combining power of the plasma, nor the change in the pH of the blood.

Section of Surgery, February 3, 1928

THE EXTENSION OF THE SURGERY OF NEOPLASTIC DISEASES BY ENDOTHERMY

(ABSTRACT)

GEORGE A. WYETH

Some seven years ago the writer, dissatisfied with the results obtained in the surgery of malignancy, and moved by Doyen's conclusion that: "Of all means employed in the destruction of pathological lesions the only certain method is that of heat," went to electrotherapy to find the best method of inducing heat in the tissues.

There was a rich literature devoted to the methods and results of the application of high frequency currents to disease and, although considerable patience was needed to untangle the confused nomenclature of its presentation, the investigator was repaid by the findings of accomplishments covering a period of more than twenty years.

Doyen and Nagelschmidt had demonstrated so long ago the high value of electric coagulation in the destruction of malignancy. Clarke, of Philadelphia, had for more than fifteen years, used with brilliant success the lighter current to accomplish that desiccation by which lesions of the more delicate tissues may be destroyed without injury to surrounding areas. It was impossible to doubt the authenticated results which these men and many others presented—results far outweighing the unwarranted claims by which less scientific students had brought criticism upon the whole field of electro-therapeutics.

Our own interest in what has been developed as endothermy was greatly stimulated by our experience with a case of tumor of the bladder. The usual suprapublic incision was made by the scalpel. The growth was exposed by electric light in the bladder and was desiccated in situ

and removed. The bladder was then sutured in the usual way, without drain. After three months, cystoscopic examination showed the site of the lesion so free that it was difficult to be sure just where the growth had been. Along the line of the scalpel's incision, however, were three carcinomatous nodules. There could not be a more graphic picture of the beneficent action of the high frequency current as contrasted with the scalpel's lack of protection against the implantation of malignant cells. The need of perfecting a cutting current which should extend surgery's usefulness as a weapon against neoplastic growths seemed urgent.

From the realization of this need the perfected cutting current, the endotherm knife, was developed and presented before the Surgical Section of the State Medical Society in Rochester, April, 1924. In reporting our work tonight, we realize that it is not conclusive. Sufficient time has not yet elapsed nor have we had a sufficient number of cases for us to offer final results. The work is, however, indicative and on this ground it is presented.

As we hereafter discuss the methods by which results are achieved it will be observed that a sound surgical training is the basis of its successful employment. But equally important is a thorough knowledge of the precise use of the currents for they differ widely in character and effect.

In the treatment of localized malignancy which can be immediately removed we no longer use X-Ray or radium. They are time-consuming, uncertain in action and in this type of case should not be employed.

Recent knowledge and Broders' classifying of neoplastic growths on the basis of cell differentiation or degree of malignancy have shown the folly of generalization in treatment. Although surgery still remains the cancer sufferer's chief hope, it is as wrong to cut all cancers as it is to treat all cancers by physical measures. Grades 1 and 2, being less malignant, are more responsive to treatment and can be reached by a wider range of curative measures than can Grades 3 and 4, which offer far less hope if attacked solely

by conventional means. The value of this to the patient is very great. So many cases of cancer, however, are already beyond the reach of the scalpel when first seen by the surgeon that there is urgent need for a new method. To illustrate:

In 1925, Simmons of Boston, reporting from the Collis P. Huntington Memorial Hospital, found that of 103 cases of carcinoma of the tongue who applied for treatment, 76 were inoperable. Similarly, Judd and New, of the Mayo Clinic, reported that of 303 cases of carcinoma of the tongue which came under their observation between January 1, 1910, and January 1, 1922, 186 (61.05 per cent.) were inoperable. To seek to limit the number of these so-called inoperable cases merely by urging early examination and earlier operation is not enough. There is need of an extension of surgery's applicability that will not only reach a much larger percentage of cases as they apply but will reach them with more lasting benefit.

Judd has since said: "For growths too extensive for radical surgical removal diathermy offers the best prospect." We go further and suggest that a remedy which offers the best prospect in cases too extensive for scalpel removal offers also the best prospect in cases not too extensive for scalpel removal.

In endothermy we have three procedures:

To desiccate the malignancy; to coagulate the malignancy; or to excise the malignancy with the endotherm knife which seals lymphatics as it cuts. There is also a technic of combining the use of the coagulating and the cutting currents to make possible the destruction of malignancy *in situ* and its excision as a dead mass, instead of as a group of viable cells. This greatly reduces the danger of metastasis and the likelihood of recurrence, and the operation can be done without hemorrhage. These several procedures are not interchangeable; each has its own indication and should be learned and used accordingly.

It is in the field of mouth carcinoma that endothermy finds its greatest usefulness. Danger of mechanical transplantation is minimized, hemorrhage and surgical shock are eliminated and there is an immediate sterilizing effect of intense heat upon the foul, painful area which permits the early return to normal diet. In all cases of cancer of the oral cavity we realize that the great problem lies in the neck. In the brief time allotted to this paper there can be no discussion of detailed treatment. We would only say that our experience has lead us to share the view of Mr. Clayton-Greene and his English confreres. Mr. Clayton-Greene says: "I am becoming more and more doubtful as to the value of big gland dissections practised in cases of carcinoma of the tongue. If the glands are not involved the operation is unnecessary and if they are extensively affected it does not seem to prevent recurrence."

To those exceptional cases, melanomas and the various malignant lesions which by their very extent or by the depth of their involvement must be classed as inoperable by any careful user of the scalpel, endothermy greatly extends surgery's usefulness. Its results cannot be dismissed as the accomplishment of a cautery and endothermy should not be spoken of as cauterization. There is no burning. The applicator is always cold when applied, the heat coming from within the tissues in response to the many oscillations of the high frequency current.

In tumors of the breast endothermy finds further opportunity for service. In the very early cases of breast tumors, where there is but the presence of a suspicious nodule, we use a very fine needle for the cutting current and incise down to the small tumor. Gradually elevating it by working around it, we remove the nodule without opening the lymphatics. We are thus enabled to make definite microscopic diagnosis without jeopardizing the patient through mechanical dissemination. In discussing radical amputation of the breast with the endotherm knife and without ligatures, Kelly of Baltimore welcomes changes

which tend to shorten the length of the operation and decrease the handling of the wound while protecting the patient from the likelihood of infection and the dissemination of tumor cells. He says: "We believe we have such an improvement in the radical breast operation in the new endotherm methods."

In advanced carcinoma of the breast, particularly of the fungating variety, by the combined technic of bipolar endotherm and the endotherm knife we perform a two-stage operation, which isolates and immediately removes the offending part first and, later, cleans out the axilla and cares for the supraclavicular space.

There is time to speak but briefly of the cases of malignancy located in cavities which may be made accessible, such as malignancy of the antrum, larynx, bladder. One would say in general that it is our custom to open the cavity with the endotherm knife, expose the neoplastic growth to full view and proceed to destroy and remove it after the indicated technic of endothermy. Surely one is justified in first offering to his patient this alternative of electrothermic destruction before submitting him to the crippling operation of complete laryngectomy for a beginning carcinoma.

The procedure is a new one and in recommending new methods and the modification of old methods to the attention of the profession we would quote what Dr. Lewis McArthur so effectively said at the meeting of the American Medical Association in St. Louis. Urging upon his colleagues the importance of deviating from accepted surgical axioms and even, in rare instances, operative procedures at variance with established surgical teaching, Dr. McArthur said: "Otherwise surgical judgment is banished and surgery becomes a set of formulas; the surgeon disappears and there remains only the operator."

FUNCTIONAL RESTORATION AS AN ELEMENT IN FACIAL REPAIR

J. Eastman Sheehan

Perhaps one ought to apologize for reminding a gathering of surgeons that consideration is to be given to function in any case of surgical intervention. There is some excuse for doing so, however. There is a steadily increasing literature about repairs of various kinds effected in that area of high visibility and I suppose all of us, when we glance at such articles, at once make the comparison between the first and the last photograph with little more in mind than the degree of betterment in appearance that has been attained. Gradually we come to think that the esthetic improvement is the whole object of the procedure; so that if we go on long enough we are apt to fall into serious error as to the quality of the surgery that is demanded, the same error into which the general public is misled by reckless publicity and also by the actual methods of some enterprising people whose practice is very little concerned either with function or with the nature of the tissues with which they have to deal.

The truth is, of course, that function and appearance are very closely allied. One may say that as a rule failure of function is caused by some disfigurement or itself produces disfigurement. And the converse is equally significant; restoration of function conduces to esthetic improvement, and may even, in extreme cases, go far to compensate the patient for such degree of disfigurement as may remain after all possible has been done.

This leads to another consideration. It is axiomatic that any condition of the kind we have here in mind is to be diagnosed in terms of the loss, whether that loss effects tissues or function. But there is more. There may be loss that is intangible without being on that account any less real. Facial disfigurement may carry with it loss of the means to make a living; not because the capacity has been lost but because there is an unwillingness to afford to the

victim the opportunity to work under the view of others. They may be capable of service but they are ineligible for employment. Or again, the person so disfigured may be so self-conscious as to shrink from all normal social contacts, or may be shunned by those whose society would be agreeable. Loss of the prospects of marriage, which is no small matter in some personalities, may be occasioned by what, from the surgeon's viewpoint, might be considered a very minor disfigurement. The face brings into the problem the relation of the individual to society, and while that is not commonly thought of as being within the range of surgical concern, actually it is.

Evidently, therefore, everything within the arsenal of reparative surgery is to be drawn upon, according to the need, with a view primarily to the restoration of function, and the resulting stimulus to ingenuity is one of the things that imports an element of fascinating interest into the handling of every case of this nature.

Let me indicate the variety of these expedients by citing a few instances.

Customarily, we think of blockage of the airways as the only interference with function in relation to the outer nose, and in the same way we think of the septum as the seat of the dysfunction. But there are certain distortions of the columella which materially impede inspiration, and anything that lessens the flexibility of the muscles about the nostrils also constitutes a serious impediment. Traumatic injury frequently so flattens the nasal bones that there must be an alteration in the nature of the posterior channels. As one studies the variety of injuries resulting from a heavy blow on the nose, he comes to see that the best expectation of restoring normal function, not merely the partial function associated with the passages nearest the septum, is to be realized by restoring all the elements of the outer nose as nearly as possible to the normal positions. So there is an advantage in separating the nasal bones at the maxillae and raising them to the old level, as also in reducing the size of the hypertrophied lower lateral

cartilages. It is a fortuitous coincidence that the excised morsels of the alar cartilage serve very nicely to prolong the new line of the dorsum established in the upper quadrant by raising and re-aligning the nasal bones. There is undoubted satisfaction in observing the gradual reconstitution of the nose as the septum, columella and tip are restored by simple expedients, but there is still greater satisfaction in knowing that the better the nose looks after these readjustments the better is the functional restoration also.

Or suppose we consider the conditions in the orbit from which, in whatever manner, the eye has been removed. In the normal state, the eyelids are insured freedom of action by the flexibility of the conjunctival membranes. Destruction of these results in adhesion between the elements within and without the orbit, and so long as that condition persists there cannot be even a semblance of function as regards the lids. But once an epidermic graft, properly cut and properly placed, has been substituted for the conjunctival sac, the lids can be made to regain their mobility. If the nerves of the lids have been conserved, as very often they can be, the lids, after any number of devices for repair have been completed, may function almost as well over a prosthesis as they did over the eye itself. That account may sound like a commonplace of the clinic, but for the patient there is the additional interest that he is no longer refused employment because of his repulsive appearance.

In this region of the orbit there are two conditions nowadays encountered with rather disturbing frequency. One is the typical windshield wound, the other the typical knife wound as developed by the antagonisms of certain city groups with the old world traditions. In both instances vertical incision of the strands of the orbicularis muscle conduces to lagophthalmus as well as producing disfigurement. A very delicate plastic procedure indeed is the regroupment of the muscle strands across these wounds; but once that is done and the skin cover is returned both the functional and the esthetic restoration has been achieved.

Perhaps it may be interesting to note other instances in which the desire to at least simulate function has led to some manipulation of muscle elements. One patient had suffered loss of all the tissues from and including the angle of the mouth to well outward toward the ear. We succeeded in covering that defect by a double skin flap, one for lining and the other for cover. Joining the lips in that way left much to be desired from the viewpoint of mouth function. This was partly remedied by manipulation of the muscles of the upper and lower lip, giving a pretty fair balance at that buccal angle for the action of the muscles constituting the orbicularis oris at the other angle. Unlike the orbital orbicularis, which is an independent muscle, the orbicularis oris is largely made up of the terminal strands of other muscles, so that by utilizing these other muscles its mechanism can be rather closely simulated. In the case mentioned, this principle was extended a little further, strands of muscle carried down between the inner and the outer skin of the face cover conferring some resiliency upon that part.

In another of these cases, involving, this time, almost the whole of one side of the face, the skin cover was given support by insertion of bands of fascia which, being attached superiorly to the temporal muscle, not only served as a stay to the inert skin tissues but also, as the action of the muscle influenced the fascia, effectively simulated muscle movement on the cheek.

Another very interesting application of the tensile and resilient properties of fascia is in relation to the correction of some of the consequences of unilateral paralysis of the facial nerve. Since the live muscles on one side of the mouth are deprived of the normal antagonisms by which symmetry is established and maintained, distortion follows, with some degree of dysfunction. What is required is to replace the antagonism, and this can be done, with considerable effectiveness, by means of fascia bands carried to locations near the mouth and then drawn up and anchored in the tissues forward of the ear. It is the

restoration of something like a functional balance that underlies the esthetic correction in these cases.

In most of these instances, concern for function is to a greater or less degree incidental. But where, for example, the state of the tissues has produced intractable or even permanent trismus, restoration of function becomes the first of all concerns. The condition is produced by scarred and contracted membrane oftener than might be thought, and the flexibility of the membrane is impaired, it is useful to note, not only by disease but often by the devitalizing effects of the ray or radium treatments by which it is sought to check the disease. One finds, for example, after many such treatments of an angioma, that all the tissues about the growth have been rendered incapable of functioning, only the tumor itself remaining indifferent to the repeated attacks. Extirpation of the tumor is necessarily accompanied by excision of all the useless membrane and its replacement, after release of the trismus, by some material which will not act again to immobilise the jaw. This is another of the many emergencies in which recourse may be had, with all confidence, to the epidermic graft. In practise there is no area too large for it to cover and there is almost no surface on which it will not "take." Sometimes it may be necessary to keep it on stretch for a time, to obviate the possibility of shrinking and the effects of shrinking that can be foreseen, but the time is well spent.

It is hardly necessary to enlarge upon the interference with function that is involved in the presence of contractile scar, whether produced by burns or by other injuries. Obviously, it limits by its presence the functional action of the tissues it overlays, and that action can only be restored when the tissues are given a covering under which they can freely move. Here we enter the field of skin grafts in general, epidermic, free full-thickness, tubed pedicle and all the other variants. It is a field where experience and skill are demanded, and where the esthetics

of the end result are of almost paramount importance. The patient, whose face is to be exposed to the merciless gaze of society, is entitled to the best that can be done for him.

We may leave that phase of the subject with only the remark that unless due regard is had for function the esthetic betterment will not materialize, or will not be permanent, whereas if function is safeguarded improvement of appearance is vastly facilitated.

And may I conclude by suggesting that practitioners of one and another branch of physiotherapy might do well to give a little more thought than perhaps some of them do give, to the probable consequences of devitalizing the tissues with which they have to deal. With the consequences of disease and accident we must expect always to have to deal, but there is surely a momentous significance in the fact that plastic or reconstructive surgery now has to cope with a great variety of dysfunctions and disfigurements that originate in this field of therapeutics.

Section of Neurology and Psychiatry,
February 14, 1928

Symposium on Disorders of the Skin, Heart and Alimentary Canal Dependent upon Disorders of the Central Nervous System

SOME CENTRAL CONNECTIONS OF THE VEGETATIVE NERVOUS SYSTEM

SMITH ELY JELLIFFE

Dr. Jelliffe first spoke of the importance to internal medicine of a knowledge of the structures of the diencephalon. Here are to be found the chief coördinating centers for the vital functions of the human body which underly the *vis medicatrix naturae,* as well as the main regulators of metabolism.

He demonstrated by lantern slides a restricted portion of this important field, showing the main vegetative nuclei and their connections with the rest of the nervous system. He spoke of humoral hypotheses as "autistic thinking." They explain nothing. Only a knowledge of the neural mechanics can show how the body as a transformer and deliverer of energy works. Most important links in this chain are found in the human diencephalon. Bodily health, the sensation of well-being, and definite metabolic functions, such as thermal regulation, electrolyte balance, tistue tension are chiefly controlled at this level of the nervous system. These controls are mostly automatic and beyond conscious control, *i.e.,* they belong to the primitive unconscious processes. There are, however, definite cortical connections in higher animals. These predicate the fact that the automatic processes may be disturbed through higher cortical, *i.e.* symbolic, representations. In this manner it can be seen how "fear" operates to disturb the "well-being" of the body and can interfere with the *"vis medicatrix naturae."* Dr. Jelliffe confined himself to the anatomical substratum of complicated psychical processes.

NEUROGENIC AND PSYCHOGENIC DISORDERS OF THE SKIN*

JOSEPH JORDAN ELLER

The modern dermatologist does not look upon the skin as an organ *sui generis*, diseases of which have no influence on other parts of the body, or vice versa. The skin and nervous system are closely related. In fact, it is through the medium of the nervous system that the skin performs its varied physiological activities. The skin forms the protective covering of the body. Distributed over its surface are nerve fibers of pain, temperature and touch; and the body adapts itself to changes in its environment by means of these fiber reflexes.

Physiologists in the past have taught that the regulation of the body temperature by the skin is effected by the blood supply and sweat secretion. There is a newer point of view regarding the functions of the skin. In an editorial on the sweat glands in the *Journal of the American Medical Association*, February 14, 1925, the statement was made that "the skin plays a significant part in temperature control through its ability to conduct heat and evaporate water." All of the functions of the skin mentioned above are under nervous control.

In a large number of patients suffering from skin diseases one finds pathological changes in other organs; for example, certain skin disorders have a definite relation to organic disturbances of the central or peripheral nervous system. On the other hand, skin patients show psychic changes, varying from slight nervous disturbances to pronounced psychoses.

The epidermis and the central nervous system develop from the ectoderm. Damage to the latter or alterations in its embryonal development might produce changes from the normal in the skin as well as in the central and peripheral nervous system. The skin may be looked upon as

*From the Department of Dermatology and Syphilology, New York Post-Graduate Medical School and Hospital. Service of Dr. George M. MacKee.

an organ of sense, which is in continuous contact with the brain, by way of the nervous system. It can thus be seen that certain disturbances of the nervous system, either organic or functional, might produce alterations from the normal in the skin.

In functional disturbances of the nervous system, such as in hysteria and neurasthenia, patients seem easily to be able to simulate or to suggest to themselves, diseases of the various organs, included among which is the skin; and the latter is a favorite location for the complaints of neurasthenics. Secondly, skin symptoms may occur, simultaneously, in a neurotic individual as the result of the neurosis which causes alterations in the gastro-intestinal functions. The sympathetic nervous system is the seat of important functions for the mind as well as for the skin. The internal secretions, whose influence may be conveyed by the sympathetic nerves, may produce mental as well as skin changes, and it is in this way that dermal and psychic diseases often occur jointly as symptoms of the same cause.

It seems at times that there is a connection between psychic alterations and certain trophic and pigmentary disturbances of the skin. This might be explained in the fact that the emotions may exert an influence on the organs of internal secretion, following which endocrine disorder, there may be various pigmentary and trophic disturbances of the skin.

The study of internal secretions and their influence on the psyche and the whole organism have suggested immense explanatory possibilities for a large number of pathological changes, particularly in the skin. Many vasomotor disturbances appear only as an expression of irritation of blood-vessel innervation by hormonal influences. In pronounced emotional states, for instance, there may occur an enlargement of the thyroid gland, hypophysis and increased adrenaline secretion, etc. (Pel, Katsch, and others cited by Gadelius). Strandberg [1] says that a congenital disorder of the autonomic nervous system may

cause various skin diseases produced by trophoneuroses and angioneuroses.

Coincidently with vasomotor alterations one finds abnormal sweat secretion. In syringomyelia, hysteria, Basedow's disease and other conditions there is often increased perspiration.

It is beyond doubt that the hair may turn gray prematurely by worry and trouble, and there have been reports that hair has turned white over night, following sudden shock. This has been doubted by various observers, among whom are Hebra and Kaposi. Strandberg [1] cites a case of Reinhard, a patient suffering from manic depressive insanity who had alterations of the color of her hair occurring rather regularly. During the stuporous period the color of her hair was light yellow, while the hair became darker, with a golden red tone during the state of excitation. The changes in the color which occurred on the tips of the hairs appeared during the first day of the patient's mental change.

Total loss of hair following traumatism of the central nervous system has been reported in the literature as well as following psychic shock. Strandberg says that psychic factors undoubtedly play a part in certain cases of alopecia areata. He refers to the work of Rock, Poehlmann and Strandberg. O'Donovan, [2] in his monograph, also attributes a psychic condition as being one of the main etiological factors of alopecia areata. Strandberg quotes a case of total alopecia in a patient with dementia praecox. In relation to the occasional remissions of the mental disease, the hair began to regrow.

Changes in the nails may occur from psychic, as well as from nervous disorders. Oppenheim, [3] Strandberg, [1] Heller and others mention this, and Heller [4] has devoted many pages in his monograph on diseases of the nails to the various disturbances of the nails due to certain diseases of the nervous system.

Heller says that various trophic disturbances of the nails occur, particularly in insane persons. He mentions

that Papillon found nail disturbances in 250 out of 1,050 insane patients examined. Heller observed that nail changes are also frequently found in delirious, epileptic and paralytic patients.

The following table shows the great variety of nail lesions that may result from injury to the peripheral nervous system. This table is founded on the observations of Heller, Cassirir, Oppenheim and others.

General Symptoms Occasionally Observed in the Nails After Injury of Peripheral Nerves

EARLY STAGE OF NERVE LESION

1. *Hypertrophic Symptoms (increased nail growth)*
2. *Atrophic Symptoms*
   a. Decreased nail growth
   b. Thinning
   c. Falling out of nails
   d. Loss of lustre
3. *Deformities,* such as:
   a. Striation
   b. Bending
   c. Ridging (longitudinal; transverse)
   d. Beading (pearl formation)

LATER STAGE OF NERVE LESION

1. *Atrophy of Nails*
2. *Arrest of Nail Growth*
3. *Decrease in Size*
4. *General Deformity*
5. *Falling out of Nail*
6. *Loosening of Nail*
7. *Ulceration of Nail Walls*
8. *Bleeding underneath Nail*
9. *Ridging (longitudinal; transverse)*
10. *Hardening*
11. *Onychogryphosis*
12. *Fusion of Nail (nail-bed sign—Alföldi)*
13. *Longitudinal and Lateral Curving of Nail*

Among the pigmentary changes which occur in the skin directly or indirectly from psychogenic or neurogenic disturbances may be mentioned vitiligo (or loss of pigment in patches), chloasma (increased pigment in patches), von Recklinghausen's disease, and the changes in pigmentation of areas of the skin affected with scleroderma and other skin diseases resulting from trophoneuroses.

Vasomotor and trophic symptoms of the skin may be found in many insane persons. Acrocyanosis, abnormal hair growth, anomalies of the sweat and sebum secretion have been described by some observers.

The joint occurrence of congenital malformations in the skin (nevoid diseases) and psychic inferiority has frequently been reported. Among some of these conditions may be mentioned von Recklinghausen's disease, adenoma sebaceum, marked ichthyosis, epidermolysis bullosa hereditaria, alopecia congenita, congenital nail changes and extensive pigment anomalies (Strandberg,[1] also Bettmann[5]).

The causes of these combined malformations and psychic abnormalities of the skin are possibly due to injuries of the ectoderm which occurred during fetal life. Consanguinity and degenerations caused by alcoholic abuse and syphilis may play a role in some of these cases.

Various factors influence the blood-vessel tonus, such as the psyche and the vegetative nervous system. These may both be influenced by the internal secretions. When a psychic disturbance affects the blood-vessel tonus, it does this by way of the vegetative nervous system.

Thus it can be seen that it is difficult to classify skin disorders resulting from disturbances of any part of the whole nervous system. Dermatoses which manifest themselves as vasomotor and trophic disturbances do not, as a rule, represent a clinical entity. They are usually secondary to various organic and functional nervous disorders.

The organic lesions of the central and peripheral nervous system are manifold and they may produce various skin conditions. In syringomyelia we find trophic disturbances of the finger-nails and skin of the hands; in tabes dorsalis, perforating ulcers of the feet; in leprosy, trophic disturbances of the skin of the hands, as a result of the involvement of the ulnar nerve; various trophoneuroses and angioneuroses of the skin resulting from traumatism to the brain or spinal cord; etc., etc.

When the organic lesions of the nervous system produce skin manifestations they do this through the interaction of the central and peripheral nervous system and the vegetative nervous system.

Skin diseases of nervous origin are often regarded under two main headings, such as psychogenic and neurogenic. As can be seen from the foregoing, this may easily lead to confusion, for no such sharp distinction can be made. Many of these skin disorders may be both of psychogenic and neurogenic origin. Again. disturbances of psychic origin, in exerting their influence on the skin, do so through nervous pathways. Examples of this are pallor from fright, blushing, horripilation (erection of the hairs of the skin), cutis anserina (goose-flesh), and changes in the sweat secretion. For these reasons, and as a practical working basis, I have put the neurogenic and psychogenic disorders of the skin into five main groups, as follows:—

Group I

Skin Disorders Due Exclusively to Psychic Disturbances

1. *Dermatitis Factitia* (Mythomania of Dupré) (deception always practiced)	Various degrees of dermatitis from a simple erythema to the so-called "neurotic" gangrene.

2. *Neurotic Excoriation* (Dermatothlasia) (no deception intended)
3. *Trichotillomania*
4. *Trichokyptomania*

} Compulsion neuroses

5. *Dermatophobias*
   a. Syphilophobia
   b. Parasitophobia
   c. Cancerophobia ("burning tongue," etc.)
   d. Bromidrosiphobia
   e. Rupophobia
   f. Peladophobia

Group II

SKIN DISORDERS FREQUENTLY DUE TO PSYCHIC DISTURBANCES (ALTHOUGH NOT EXCLUSIVELY)

1. *Urticaria*
2. *Angioneurotic Edema* (also in group V)
3. *Erythema* (may later lead to rosacea)
4. *Pallor* (sudden)
5. *Horripilation*
6. *Cutis Anserina* (goose-flesh)
7. *Pruritus* (cutaneous; ani; vulvae)
8. *Tatoo Marks* (disputed)
9. *Changes in Sweat Secretion* (hyperhidrosis; hypohidrosis)
10. *Paresthesias* (hyperesthesia; anesthesia)
11. *Pemphigus Hystericus*
12. *Alopecia Areata* (also in group V)
13. *Lichen Planus*
14. *Certain Eczemas, such as those due to Allergy* (also in group V)
15. *Dermatitis Herpetiformis*
16. *Psoriasis*
17. *Dermatitis Dysmenorrhoeica* (also in group III)

Note: Items 11, 12, 13, 14, 15, 16, 17 disputed by most observers.

Group III

Skin Disorders Frequently Associated with Psychic Disturbances Although not Necessarily Due to Them

1. *Congenital Malformations* (nevoid diseases)
   a. Von Recklinghausen's disease (also in group IV)
   b. Adenoma sebaceum (Pringle)
   c. Marked ichthyosis
   d. Alopecia congenita
   e. Cutis verticis gyrata (microcephalic idiots)
   f. Epidermolysis bullosa hereditaria
   g. Albinismus
   h. Congenital pigmentation anomalies
2. *Trophic Disturbances of the Hair and Nails* (also groups IV and V)
3. *Pigment Anomalies, (particularly Vitiligo)* (also groups IV and V)
4. *Pellagra* (also in group IV)
5. *Pellagra in Alcoholics* (Pseudopellagra)
6. *Beriberi*
7. *Scurvy*
8. *Erythredema Polyneuritis* (Acrodynia) (Butler, also Foerster)
9. *Erythromelalgia* (also in group V)
10. *Herpes Simplex* (disputed) (also in group IV)
11. *Dermatitis Dysmenorrhoeica* (disputed) (also in group II)

Group IV

Skin Disorders Due to or Associated with Organic Disturbances of the Central or Peripheral Nervous System

1. *Herpes Zoster*
2. *Syphilis* (perforating ulcer of tabes dorsalis)
3. *Trophic Disturbances due to Syringomelia*
4. " " " " *Myelitis* (infectious, etc.)

5. *Trophic Disturbances due to Multiple Sclerosis*
6. " " " " *Tumors of the Central or Peripheral Nervous System*
7. " " " " *Traumatism of the Central or Peripheral Nervous System*
8. " " " " *Epidemic Encephalitis*
9. *Trophic Ulcers due to Arteriosclerosis of Blood Vessels of Spinal Cord*
10. *Leprosy* (also in group V)
11. *Von Recklinghausen's Disease* (also in group III)
12. *Pemphigus* (disputed)
13. *Pellagra* (disputed) (also in group III)
14. *Herpes Simplex* (disputed) (also in group III)

(NOTE:)—When skin breaks down (trophic disorder) in the presence of a mental disease, it is evident that the mental disease is due to an organic disturbance.

Group V

SKIN DISORDERS OFTEN ATTRIBUTED TO DISTURBANCES OF THE VEGETATIVE NERVOUS SYSTEM (ANGIONEUROSES AND TROPHONEUROSES)

1. *Angioneurotic Edema* (also in group II)
2. *Scleroderma*
3. *Raynaud's Disease*
4. *Erythromelalgia* (also in group III)
5. *Progressive Facial Hemiatrophy*
6. *Certain Eczemas, particularly of the Allergic Type* (also in group II)
7. *Alopecia Areata* (also in group II)
8. *Trophic Disorders of the Skin found in*:
   a. Syringomyelia
   b. Multiple sclerosis
   c. Myelitis (complete and incomplete)
   d. Tumors of the central or peripheral nervous system
   e. Traumatism of central or peripheral nervous system

f. Epidemic encephalitis
g. Arteriosclerosis of the blood vessels of the spinal cord
h. Leprosy (also in group IV)

While there is concurrence of opinion in regard to the interrelation of the psychic conditions and skin disturbances generally, many divergent views are held by observers concerning various specific disorders.

The etiologic factor in a number of skin diseases is still unrecognized. Their occurrence coincident with psychogenic disorders, however, is frequently noted. Although it is impossible to show, by any palpable means, a direct connection between neurogenic, psychogenic and dermatological conditions, it is likely that a study of their joint occurrence, with a view to their possible causal relation, may help in solving many a perplexing problem.

Influenced by many of the outstanding articles in the literature, and as a result of personal observation and experience, the writer has divided these conditions into five groups, according to the plan given above. They will now be discussed under these headings:

Group I

Skin Disorders Due Exclusively to Psychic Disturbances

The fact is recognized that blood-vessel tonus is regulated by several factors, among which may be included the psychic element, the vagotonic and sympathetic nervous systems. These, in turn may be influenced by the internal secretions. This vascular influence, of course, is exerted in the skin as well as in all other organs of the body. It therefore seems logical to suppose that every skin disease which results from a functional or organic disturbance of the central or peripheral nervous system develops through the action of the vegetative nervous system. Viewed in this way, it seems quite impossible to disassociate these various branches of the organism.

The conditions under discussion in Group I comprise

disorders of the skin due exclusively to psychogenic or neurogenic conditions. Included in this group are:

a. Dermatitis factitia (mythomania of Dupré).

b. The Compulsion Neuroses. These include (1) dermatothlasia (neurotic excoriation); (2) trichotillomania; and (3) trichokyptomania.

c. Dermatophobias, namely: (1) syphilophobia; (2) parasitophobia; (3) cancerophobia ("burning tongue", etc.); (4) bromidrosiphobia; (5) rupophobia; and (6) peladophobia.

A great proportion of the functional neuroses predispose to various skin affections. It is these disorders which comprise Group I.

The term *dermatitis factitia* (also called feigned eruptions) includes numerous conditions in which the varying degrees of skin disorders range from a simple erythema to "neurotic" gangrene. Dupré classifies the "feigned eruptions" among the mythomanias. *The patients always practice deception.* In these patients various methods may be used in order to produce lesions, among the most frequent being the application of chemicals, such as carbolic acid. As a rule, the artifical dermatitis can be recognized in spite of the patient's deceptive history; but at times, even the well-trained dermatologist may be misled. Many cases are cited in the European literature where amputation of one or more limbs has been performed on patients presenting large areas of gangrene of "idiopathic" origin, which cases later were proven to be due to application of caustics by the patient.

Neurotic excoriations (dermatothlasia) are lesions in the skin produced by the patient, *in which no deception is intended*, and in which he or she has an uncontrollable desire to pick, scratch or to injure the skin in other ways. Very often the patient imagines that parasites are in the skin and that he must pick them out.

Concerning the neurotic excoriations Klauder [6] states:

"Under this name, Fournier [7] first described a morbid state characterized by an uncontrollable desire of the

patient to scratch or rub one or more areas of the skin. This practice may give rise to excoriated lesions. Fournier thought perhaps it was an atavistic expression comparable to the scratching of certain animals and birds and comparable also to the self-mutilation of certain psychopathic patients . . ."

"In the same category as dermatothlasia may be placed self-inflicted lesions of the skin grouped under the heading neurotic excoriations. These have been described under different names by a number of writers, notably so by Adamson, [8] MacKee, [9] and Pusey and Senear. [10] Brocq's excoriated acne of young girls is also placed in this group. The involved area is usually at first pruritic and may have been the site of some insignificant skin lesion. As a result of what is apparently an uncontrollable desire to pick or dig with the finger nail or some other agent, oval or irregularly shaped excoriations or ulcers are produced. Pigmented areas and scars, the result of involution of former lesions, may also be seen. In the excoriated acne of young girls, manipulation is directed at the existing acne lesions involving the face.

"Neurotic excoriations are distinct from a factitious dermatitis. Self-inflicted lesions of the skin, produced for the purpose of deception, are seen in certain hysterical young women, the psychogenesis of which is to arouse sympathy, and also in malingerers. In the condition under discussion there is a clear recognition by the patient of the unreasonable nature of the act. In view of this and since it manifests a defective self-control, it constitutes a psychasthenia, other evidences of which may be manifested.

"Neurotic excoriations exist in a variable degree of severity. The milder cases are, of course, more amenable to treatment with psychotherapy which is directed at the psychic fixation by distraction and voluntary reeducation, or more properly, by autoreeducation. Treatment, however, in a large measure, depends on the nature of the psychogenesis. Self-inflicted lesions of the skin, grouped as neurotic excoriations, have a variable psychogenesis.

Some, perhaps, are an expression of a tic, others an expression of a phobia. Still others may be among the topalgias of Brocq, or among Janet's *l'obsession de la honte du corps.* In the latter cases, manipulation is performed as a result of the anxiety of the patient to effect a disappearance of the lesion, which occasions in the patient's mind an obsession of shame. This particularly applied to cases of excoriated acne in young girls."

Trichotillomania (the plucking out of hair) and *trichokyptomania* or *trichorrhexomania* (the habit of breaking the hair against the finger-nail) may be considered along with the neurotic excoriations as being a compulsion neurosis in which the patient does not intend to practice deception and gives a history of having an uncontrollable desire to produce the conditions just described. A condition of this type may be lead to atypical, patch-like alopecias which may cause much confusion in diagnosis. Oftentimes these hairs are swallowed, subsequently leading to occlusion of the intestine; 108 cases of this type have been reported by Davis.[11] Those subject to *trichotillomania* usually pull out the hair without being conscious of the act, similarly as in biting the nails. Some patients state that the pulling out of the hair is caused by itching of the scalp; in others a plausible cause is missing. On the whole, it is found in hysterical individuals and, according to Strandberg, was observed by him in two children, as young as two and eight years of age respectively. Another interesting finding consisted in the discovery that frequently one or several persons in the families of those addicted to trichotillomania were known to suffer from psychic inferiority, psychosis, struma and mania. *Trichokyptomania* is evidently less frequently recognized than trichotillomania, little attention having been given to the former in the literature.

On the other hand, the *dermatophobias* seem to be discussed at greater length by the various investigators. All types of phobia are encountered in medical practice, producing symptoms in various organs, such as "nervous indigestion," diarrhea, nervous headache, etc. Is it there-

fore not logical to believe that the skin may likewise share with the other organs a certain quota of derangement?

It is known that the feeling of itching may decrease or disappear by suggestion. Again, almost every dermatologist has been consulted by patients who believed they were not freed from itching after a course of treatment which was considered thorough by the physician. This and similar forms of phobia are frequently so pronounced as to lead to a serious abnormal state of mind. Among the dermatophobias which have demanded sufficient notice to warrant a definite nomenclature are the following: *syphilophobia, parasitophobia, cancerophobia* (which includes the condition known as "burning tongue"), *bromidrosiphobia, rupophobia, peladophobia, etc.* The distinguishing feature of each phobia is easily suggested by each type, a further discussion of the subject being limited because of the lack of time allotted.

It seems evident from the foregoing that a better understanding of the interrelation or interdependence of psychic disorders and of disturbances of the skin is necessary; and it is apparent that there is an urgent need for improved methods in the study of the innervation of the sympatheticus and its pathology, as well as its relation to the internal secretions.

It is vastly important that the dermatologist recognize the psychogenic origin in dermatoses, for many of these conditions hardly come within the realm of dermatology. Such a patient should be treated in collaboration with a neurologist.

A description of the remaining groups, also additional bibliography, will appear in the completely published paper.

REFERENCES

1 Strandberg, James: *Psychogenese und Psychotherapie körperlicher Symptome. Psyche und Hautkrankeiten.* Edited by Oswald Schwartz. Berlin, Julius Springer, 1925.

2 O'Donovan, W. J.: *Dermatological Neuroses.* London, Kegan Paul, Trench, Trubner & Co., 1927.

3 Oppenheim, H.: *Text-book of Nervous Diseases.* Translated by Alexander Bruce, 2 volumes Edinburgh and New York, Otto Schulze & Co., 1911.

[4] Heller, Julius: *Die Krankheiten der Nägel.* 2nd ed. Berlin, Julius Springer, 1927.

[5] Bettmann, quoted by Strandberg. (See Reference 1.)

[6] Klauder, J. V.: The Cutaneous Neuroses, with Particular Reference to Psychotherapy. *Jour. Amer. Med. Assn.,* 85: 1683, Nov. 28, 1925.

[7] Fournier, H.: La dermatothlaise. *Journ. malad. cut. et de syph.,* 10: 225, 1898.

[8] Adamson, H. S.: Acne, Urticaria and Other Forms of Neurotic Excoriations. *Brit. Jour. Dermat.,* 27: 1, 1915.

[9] MacKee, G. M.: Neurotic Excoriations. *Arch. Dermat. and Syph.* 1: 256, March, 1920.

[10] Pusey, W. A., and Senear, F. E.: Neurotic Excoriations with Report of Cases. *Arch. Dermat. and Syph.* 1: 270, March, 1920.

[11] Davis, quoted by Strandberg. (See Reference 1.)

PSYCHOGENIC HEART DISEASE

JOHN WYCKOFF

Cardiac psychoneuroses may be classified as:

1. Fatigue neurosis (Neurasthenia).
2. Introspective neurosis (Hypochondria).
3. Anxiety neurosis.
4. Substitution neurosis (Hysteria).
5. Obsession neurosis (Psychasthenia).

Of these, the fatigue and introspective neuroses are extremely common. Substitution neurosis is less common, and anxiety and obsession neuroses rarely cause cardiac symptoms. Fatigue neuroses which were extremely common in the war are also seen in civil life. These patients exhibit two characteristics.

First, a history of marked nervous instability, either in the patient's family or in the past history of the patient himself, such as nervous prostration or neuroses referred to other organs than the heart. It is frequent to get histories of one or more abdominal or gynecological operations performed for the relief of long standing subjective symptom or symptoms.

Second, there is the history of an exciting cause in the patient's environment. This may be physical or mental effort, business and financial worries, family infelicities or seemingly trivial difficulties.

The unstable nervous system and the exciting cause are both always present, but in an inverse relationship; the more stable the nervous system the greater will have to be the exciting cause to bring about symptoms, and the more unstable the nervous system, the less need of an exceptional environmental trauma to produce them.

In civil life, usually only the more unstable develop this type of neurosis, though symptoms appear among individuals who appear normal, at times of marked business depression, after disasters, or after great sorrow.

The symptoms are fatigue, palpitation, precordial pain and a sensation of breathlessness. Usually these symptoms are increased by effort, and not unusually do the patients have attacks of dizziness and syncope. On examination they are seen to look worried and nervous, they talk a great deal of their symptoms, but not as much as do the introspective neurotics, their hands tremble and frequently their skin shows signs of vasomotor instability. The heart is rarely enlarged, the rate usually 100 or over, sinus arhythmia is the rule but ventricular premature contractions and paroxysmal tachycardia are not uncommon. Short systolic murmur may be present. Roentgenographic and electrocardiographic examinations are usually negative.

Many of these symptoms come from a lowering of the threshold to normal physiological processes. Often these patients have palpitation with regular hearts, not too rapid, and with normal blood pressure. Often they feel short of breath with normal respiratory rates. At other times, they have tachycardia and rapid, but usually shallow respiration.

Introspective Neuroses. Among the cardiac neuroses occurring in civil life, this is the largest group. These are patients who present some subjective or objective symptoms of heart disease, usually from an extracardiac cause, and who dwell upon the symptoms or symptom, worrying about them, collecting reports of various examinations made by different heart specialists, comparing them, worrying about the fact that the authorities differ,

consult others, and talk continuously to every one about their symptoms. Exaggerated cases of this sort own their own stethescope, keep charts of ventricular and pulse rates, make long notes of trifling symptoms which they read to suffering physicians at great length.

The symptoms which usually first call the attention of such introspective patients to their heart is usually one of the common irregularities in rhythm. A marked sinus arhythmia, premature contractions, or an attack of paroxysmal tachycardia will start such a patient; then if he consults one of the brethren who thinks all irregularities equally serious and who tells him he has organic disease of the heart, usually after only a casual examination, he is well on his way to a life of worry. The condition of at least some of these patients is due to improper interpretation of symptoms and signs by physicians.

Even after the symptoms which may have excited this type of neurosis have disappeared for years, the patient will go on asserting and believing that he has heart disease.

Occasionally as patients grow older, they actually live long enough to develop arteriosclerotic heart disease, and then there is great danger of missing the early signs of organic disease because the patient is still believed to have a neurosis. Once at least, I made such a mistake.

This type of neurosis sometimes develops in a patient with mild organic heart disease, and makes a difficult complication. Such a patient without an objective sign of heart failure, with only slightly diminished, or no diminution of cardiac reserve, but with signs of slight organic heart disease, will spend years as an invalid because of the development of a fixed idea of the gravity of his or her condition.

Patients with anxiety neurosis may have cardiac symptoms—the most usual symptom is palpitation. As White says: "These patients rarely present a problem to the internist, as the cardiac symptoms are so overshadowed by the state of tension, sleeplessness, illogical worries and inability to concentrate."

On the other hand, patients suffering from the substitution type of neuroses may develop attacks of heart pain which are very difficult to differentiate from pain in severe organic disease of the heart. Certain attacks of so-called "pseudo-angina" come to individuals as typical hysterical manifestations, and the differentiation may be difficult if the patient is first seen in the first or second attack, but usually is not difficult if the physician knows the patient and follows the course of the illness.

Obsession neuroses rarely manifest themselves by cardiac symptoms.

In the foregoing discussion, reference to etiology other than fatigue as a cause of these neuroses has been avoided. At least there must be reason for belief that there is a relationship between their cause and the endocrines when one goes over the rather remarkable glandular therapy which one finds the patients have received. Usually such therapeutic proceedures have been without control and the results obtained, if viewed objectively and with due consideration to the laws of probability, far from convincing. It has seemed to me the best results therapeutically are obtained in the following way. Accept the patient's symptoms as facts, examine him with care and thoughtfulness. Explain to him that no signs of structural disease are present, though all known methods of exploration have been used. Explain that normal physiological function may creep over the threshold of consciousness and give rise to symptoms. Explain how this threshold is best kept high. Describe the likelihood of relapse and when such relapses are apt to occur. If possible get rest, mental and physical, for the fatigue cases and be sure that it is rest that the patient is getting and not some other thing which some member of the family, or solicitous friend, thinks may do him good. Get suitable mental and physical occupation for the introspective group. Build up the general health of the patient and keep it at as high a level as possible. Avoid placebos, but treat him honestly and as an intelligent being. When needed, give simple sedatives. Under such a common sense regime many improve and live useful lives.

NEUROGENIC DISORDERS OF THE HEART

ERNST P. BOAS

The heart rate and rhythm depend on variations in the degree of excitation of its two sets of nerves. These variations are determined by reflexes passing over innumerable afferent pathways. This regulation of the activity of the heart is an adaptive mechanism enabling the heart to meet the demands placed on it by the varying activities of the body. Loss of this regulatory function may have serious consequences. Complete denervation of the heart, that is, severance of all of the extrinsic cardiac nerves, greatly restricts the activities of an animal. In dogs who have survived this operation for many months, the circulation is adequate when they are at rest, but any greater physical exertion is impossible. The animals collapse from exhaustion and there is no acceleration of the heart. The characteristic reactions to atropine and epinephrine are also lacking, and thyroid feeding brings about no tachycardia.

The afferent arcs of the cardiac reflexes may arise in almost any part of the body. They may come from the heart itself, from the lungs and other viscera, they may pass thru the segmental parts of the nervous system, *i.e.*, the cranial nerves, or the spinal nerves. Afferent impulses may also reach the vagus and sympathetic nuclei from all suprasegmental parts of the brain. One need but recall the changes in heart rate accompanying emotions and varying psychic states. No convincing proof has been offered of the existence of cardiac reflex arcs to the hypothalamus, and I believe with Francois-Franck and with Tigerstedt that the vital cardiac reflex arc passes thru the medulla and that the brain acts as a peripheral organ initiating reflexes via the medulla.

The following classification of neurogenic disorders of the heart may be attempted. Its value lies chiefly in its demonstration of the limitations of our knowledge.

A. I. Disorders of the nervous structures in the end organs

1. Vagus
2. Sympathetic

II. Disorders of the ganglionic arc

1. Vagus
2. Sympathetic

III. Disorders of the segmental arc

1. Vagus
   a. Nerve trunk
   b. Dorsal nucleus
2. Sympathetic

IV. Disorders of the hypothalmic arc

1. Vagus
2. Sympathetic

B. Disorders due to excessive or exaggerated afferent stimuli

1. Segmental
   a. Somatic
   b. Visceral
2. Suprasegmental

Cerebral (Abnormal mental states)

C. Disorders due to increased irritability of the visceral nervous system of unknown localization.

1. Constitutional
2. Acquired
   a. Infectious
   b. Internal secretory

D. Disorders secondary to neurogenic vasomotor disorders.

I know of no cardiac disturbances that may be placed in group one, two or four. Group three, disorders of the segmental arc, is represented in medical periodical literature by innumerable inconclusive case reports. There is hardly one which will stand critical analysis. Among

the conditions which were supposed to lead to vagus tachycardia were compression of the vagus by mediastinal tumors, tuberculous lymph nodes, aortic aneurysms, alcoholic neuritis of the vagus, and destruction of the dorsal vagus nucleus in bulbar palsy. Yet in practically every case there existed in addition to the nerve lesion other potent causes of tachycardia such as fever, dyspnea, toxemia or anxiety. On the other hand, neurogenous forms of Stokes-Adams syndrome have been described.

It is apparent that focal lesions of the extrinsic nervous apparatus of the heart play no significant role in the genesis of cardiac disorders. Neurogenic circulatory disturbances fall chiefly within the last three categories of our classification. The first group comprises cardiac disorders due to excessive or exaggerated afferent stimuli. Here may be grouped the simple tachycardias and occasional bradycardias associated with disease of the gall bladder, stomach, and other internal organs. Of greater import, however, are the occasional cardiac irregularities that are initiated by reflex stimuli from diseased viscera.

Of equal importance are cardiac disorders due to increased irritability of the visceral nervous system. It is often impossible to determine to what extent the cardiac disorder is due simply to increased irritability of the extrinsic nervous apparatus of the heart, and to what degree it is secondary to neurogenic vasomotor disorders, or to an increase of afferent stimuli from the brain, for, as a rule, all three factors operate together.

As a result of the disturbed innervation of the blood vessels, the capillaries and venules in the splanchnic region and in other areas of the body are dilated and a large amount of blood becomes pooled in them. Consequently, there often is an inadequate amount of blood in the left ventricle and in the arterial tree. This lack makes itself felt particularly during and after exercise and undoubtedly contributes largely to the rapid pulse, the dyspnea and sense of exhaustion which follows physical exertion.

NEUROGENIC AND PSYCHOGENIC DISORDERS OF THE ALIMENTARY CANAL

JOHN L. KANTOR

The paper dealt with anatomical and physiological considerations, general and local disorders of the nervous mechanism and presented the following conclusions:

From the view-point of the practising gastro-enterologist, a survey such as this, of the current literature on neurogenic and psychogenic disorders of digestion, yields the following impressions:

1. An increasing number of cases formerly diagnosed as "nervous dyspepsia" are shown on study by improved methods to be instances of actual organic disease of the digestive organs or of their nervous communications.

2. The autopsy findings of post-infiammatory nerve lesions in cases of digestive disorders suggests the advisibility of careful scrutiny of dyspeptic patients for evidence of past infections (such as tuberculosis) which might involve important nervous pathways in scars or adhesions.

3. The theory of autonomic inbalance occupies a prominent place in discussions of the etiology of such important digestive disorders as peptic ulcer, cardiospasm, intussusception, and congenital pyloric stenosis.

4. In some digestive conditions (intestinal tuberculosis, some cases of peritonitis), it is the sceondary nerve changes and not the primary lesions which produce the "characteristic" symptomatology.

5. The concept of "solar syndromes," with or without actual lesions in the nerve plexuses, is advanced by some writers to explain the painful phenomena in a rather diverse group of abdominal conditions.

6. Lesions of the spinal cord may produce visceral effects either directly by involving the preganglionic fibers at their point of origin, or else indirectly by affecting the

suprasegmental neurons connecting with these preganglionic fibers. The general result of destroying the superior connections is a release of the lower neuron reflexes.

7. Neural ileus is an important condition often leading to useless surgical exploration. This form of ileus may be due to lesions either in the segmental or suprasegmental arcs or to psychoses with marked depression. It is a common symptom of transverse myelitis.

8. Important centers regulating the functions of the entire involuntary nervous system are now known to be located in the diencephalon. Lesions in this region occur frequently in epidemic encephalitis, and occasionally in dementia paralytica and dementia praecox.

9. Psychic disorders of digestion are mediated through the emotions and through ideas causing conditioned reflexes. Conditioned reflexes, therefore, furnish a basis for the development of digestive habits, peculiarities and perversions.

10. The psychoneuroses are not uncommonly encountered by gastro-enterologists because the digestive symptoms are so prominent and varied. In melancholia, constipation is a particularly constant and stubborn manifestation.

Section of Medicine, February 21, 1928

THE CARDIOTACHOMETER

An Instrument to Count the Totality of Heart Beats Over Long Periods of Time

Ernst P. Boas

An instrument, named the cardiotachometer, has been devised, by means of which the total number of heart beats may be counted over long periods of time while the subject under test is actively moving about. The action current of the heart is led off through two chest electrodes, green soap serving as an electrolyte, into a specially constructed

amplifier. Leaving the amplifier, the current actuates a sensitive relay which, in turn, operates an electromagnetic counter, and simultaneously records on a moving tape.

We have repeatedly kept patients under test for from twenty to twenty-four hours, during successive periods of rest, activity and sleep. We have not yet had time to accumulate enough data to draw final conclusions on any of the phenomena that we have studied, but have made some preliminary observations that seem to be of real interest. We have run patients for long periods of time with a view of learning the range of variability of the heart rate and, in particular, its behavior during sleep.

The normal individual exhibits only a moderate variability in heart rate in response to his ordinary daily routine. During sleep the rate is from 10 to 20 beats a minute lower than when the subject is at rest, but awake. There are many people with an unduly rapid and variable heart rate. Relatively slight physical exertion or emotional excitement is followed by an unusual acceleration of the heart, so that throughout the day, particularly whenever the subject is examined, the pulse rate is rapid. During sleep, however, all of these reactions are abolished and low figures are obtained. Apparently the rate does not sink to the same low level as it does in the more phlegmatic type of person, a fact which suggests that even during sleep the vegetative nervous system of these individuals is more irritable than normal.

On the other hand, subjects of a rheumatic myocarditis with rapid heart rates show very little drop in rate during sleep. This is a valuable sign for diagnosis, and indicates that the rapid heart rate is not determined primarily by factors extrinsic to the heart. Similar observations have been made in patients with Graves' disease, as well as in those suffering from congestive heart failure.

Studies of patients with auricular fibrillation have been most interesting. In spite of the fact that in them the sino-auricular node no longer controls the heart rate, variations in heart rate far greater than in normal persons has

been found. It is well known that exercise, the administration of atropine, or, at times, an intercurrent infection, will greatly increase the ventricular rate in subjects with auricular fibrillation, and that under rest in bed the rate may become reduced. We have been able to confirm the increase in ventricular rate accompanying exertion, and have been able to demonstrate a great variation in ventricular rate during the day. Most interesting of all is the fact that in undigitalized, as well as in digitalized patients, the ventricular rate during sleep may drop 25 to 35 beats.

The possible clinical applications of the cardiotachometer are manifold. Many physiological problems, such as the response of the heart to exercise, drugs, and other stimuli can be studied. Its response during exercise can be accurately measured. As an accessory in many physiological and clinical examinations, such as basal metabolic rate and minute volume flow determinations, it is invaluable. It will for the first time give us an actual count of the total number of heart beats under the conditions and activities of every day life. It will be of particular value in determining the clinical significance of the simple tachycardias.

ANNUAL GRADUATE FORTNIGHT

The Academy is making arrangements for a series of lectures at the Academy, co-ordinated clinics, clinical demonstrations and courses in hospitals and teaching institutions of New York, on the subject of "The Problem of Aging and of Old Age."

This is to be the first "Annual Graduate Fortnight" which the Academy is arranging for the benefit of general practitioners and specialists, which will take place the first two weeks of October, beginning October 1, 1928.

It is planned to have each year a subject chosen for the Annual Fortnight which is of outstanding importance in the practice of medicine and surgery and which will be approached from every available angle with the least loss of time and the greatest possible opportunity to be offered to physicians from out of town.

A number of outstanding authorities will be invited to take part in the Annual Fortnight, and particular emphasis will be placed upon lectures and courses on the early recognition and prevention of disturbances, commonly ascribed to aging, but very often not the result of aging but its cause. Courses on functional tests of organs and systems of function such as circulation, digestion, metabolism, endocrine functions, immunity, etc., are to be offered and the relation of unrecognized forms of intoxication, chemical as well as bacteriological, to the dangers of middle age are to be specially emphasized.

TESTIMONIAL DINNER TO DR. NORRIS

On Monday evening, February 6th, 1928, the Committee on Public Health Relations and that on Medical Education gave a dinner at the Academy of Medicine in honor of Dr. Charles Norris, Chief Medical Examiner of the City of New York. The dinner was tendered to Dr. Norris as an expression of the esteem in which he is held by medical men of the community and by way of recognition of his remarkable achievements in the ten years during which he has held office. Sixty men, members of the two committees and several distinguished guests, attended the dinner, joining enthusiastically and of one accord in the eulogy of Dr. Norris.

Dr. Samuel W. Lambert, President of the Academy, acted as toastmaster. In his address of welcome Dr. Lambert briefly outlined Dr. Norris' career from his early training under Dr. T. Mitchell Prudden to the present, and started the testimonials of the evening by calling on Dr. James Ewing to tell more in detail about the early part of Dr. Norris' career.

Dr. Ewing congratulated Dr. Norris on the splendid gathering in his honor, paying tribute to the distinguished character of the group present. Dr. Ewing spoke also of Dr. Norris' pioneer work in sero-bacteriology, his connection with Cornell University Medical College, his appointment as pathologist at Bellevue Hospital, and his unusual foresight in the development of this department, an outstanding accomplishment in its day and at the time the best equipped pathological laboratory of any hospital in the country. Under Nr. Norris the work at Bellevue Hospital laboratory developed steadily, and Dr. Norris became not only technical pathologist but consultant pathologist, contributing his knowledge and advice to the Clinical Department and to the Superintendent of the hospital.

With the change from the old inefficient and incompetent pretence to legal medicine in the form of the coroner to the saner system of a unified Department of Medical Examiner, in the bringing about of which the Academy

of Medicine, through its Committee on Public Health Relations, had an important part, another opportunity came to Dr. Norris. Dr. Ewing said that this was really an event in the history of New York Medicine. In closing his remarks the speaker emphasized the importance of this branch of medicine, and of the contributions made by Dr. Norris in the course of his career in it.

Judge Joseph E. Corrigan, who presides over the Homicide Court, spoke eloquently about the work of Dr. Norris, pointing out the great improvement of the new system over the old.

The system of medical examiner was begun in Massachusetts as a State institution and became particularly developed in Boston. Dr. George Burgess Magrath, Medical Examiner of Boston, was called upon to tell of the work in that city. Dr. Magrath described the development of the system and its present status. He told of Dr. Norris' inspection of the Massachusetts system seven or eight years after its inception, praised the organization which Dr. Norris has instituted and in conclusion saluted him as "a skilled, sagacious man of science, wise administrator, honest public servant."

Another representative of the courts, Justice Philip J. McCook of the Supreme Court, was called upon by Dr. Lambert. Judge McCook spoke of the splendid work of Dr. Norris in connection with medical jurisprudence in its various phases and like Judge Corrigan commended particularly the ability of Dr. Norris to give satisfactory, impartial and competent testimony in court.

Dr. Ludwig Hektoen described briefly the historical development of forensic medicine and discussed various phases of it, including the requirements for medico-legal institutions or institutes for forensic medicine which already exist in certain European countries, but not in America. Dr. Hektoen expressed the opinion that since New York has successfully taken the first step to modernize its medico-legal work, it will eventually take the step of providing adequate training in it.

Dr. Norris said that he knew very well that his work could be improved in many ways and called attention to the needs of his service. With over 2,000 autopsies a year and the limited staff and equipment it is scarcely possible to handle the work in an accurate and scientific manner. The stenographic force is limited and the laboratory staff likewise insufficient. It is necessary to supplement the staff and salaries from private sources. Dr. Norris reiterated what Dr. Magrath and Dr. Hektoen had said about the need for training people for the service.

Dr. MacCallum expressed the opinion that there is a need for such an institute, that it should be very elaborately planned and staffed, that it should be established in relation to several universities and should be connected with the department now headed by Dr. Norris.

Dr. Dana suggested that the group present should take some action in this matter. Motion was made to appoint a committee to study the project and to report on it. The motion was seconded and carried.

The testimonials to Dr. Norris were concluded with the remarks of Dr. MacNeal who has recently conducted a survey of the Medical Examiner's service in New York City.

PUBLIC HEALTH RELATIONS COMMITTEE

SUMMARY OF ACTIVITIES

OF THE

EXECUTIVE COMMITTEE

MONTH OF FEBRUARY

1928

Among the matters which came before the Public Health Relations Committee were the following:

1. *The Proposed Dwelling Law*

After considerable study, the State Commission, consisting of members of the State Senate, the Assembly, and representative private citizens drafted a comprehensive bill modifying the existing laws on housing.

The phases of this bill which were of particular interest to the Committee were the provisions for light, air and general sanitation, which the bill makes possible in dwellings to be erected in the future.

The following resolution was adopted by the Executive Committee and endorsed by the Council of the Academy:

"The dwelling conditions in a large city are a very direct concern of all who are interested in the preservation and promotion of public health.

The factors of light, air, overcrowding and cleanliness in dwelling houses materially affect the health and efficiency of the members of any community. This is particularly true in large cities where other interests of importance may tend to run counter to that of health.

The Committee on Public Health Relations of the New York Academy of Medicine is, therefore, deeply interested in the proposed Dwelling Law in so far as it promises to bring about an improvement in the sanitary living conditions of New York City.

It is the opinion of this Committee that the proposed law does represent an attempt to take an important step

forward toward such improvement. Upon the economic effects of the proposed law relative to such matters as rentals, and land values, construction costs and the like, and also upon the practicability of such a measure we can have no opinion.

We do believe, however, that factors of health have sufficient importance to outweigh many possible economic objections.

Insofar, therefore, that the proposed law does provide for more healthy and sanitary living conditions and within the limitations above outlined, this Committee heartily endorses such provisions."

2. *Medico-Legal Work of the City*

On February 6, 1928, a dinner was given in honor of Dr. Norris at the Academy under the joint auspices of this Committee and that of the Committee on Medical Education. There were sixty-five persons present and the speakers, which comprised medical men of distinction as well as judges most familiar with the work of the Chief Medical Examiner of this city, emphasized the services rendered to the city by Dr. Norris and stressed the desirability of creating, in conjunction with his office and the universities, an institute for the teaching of legal medicine. At the present time, there is no adequate teaching offered in this important branch.

It was also pointed out that more adequate appropriation should be forthcoming from the city to make possible a larger and better paid laboratory staff.

Other matters which were considered by the Committee were:

a. Ventilation of school buildings;
b. Standardization of Civil Service requirements in relation to medical positions in the city service;
c. Poliomyelitis convalescent serum;
d. The need of study of helio- and photo-therapy;
e. Problems of street cleaning, and
f. The present organization of the Tuberculosis Admission Bureau.

PROCEEDINGS OF ACADEMY MEETINGS

JANUARY

Stated Meetings

Thursday Evening, January 5, at 8:30 o'clock

I. Executive Session
Business of the Annual Meeting
Action on amendment to the By-laws, introduced at the Stated Meeting of December 1, 1927
Election of Fellows

II. Address
On the significance of bacterial allergy in infectious diseases, Hans Zinsser, Professor of Bacteriology and Immunology, Harvard University

III. Paper
The relation of lobar pneumonia to massive atelectasis of the lung, Pol. N. Coryllos (by invitation), and George Birnbaum (by invitation)

Thursday Evening, January 19, at 8:30 o'clock

I. Executive Session

II. Symposium: Graduate Medical Education
a. An experience in university graduate medical education, Louis B. Wilson, Director, Mayo Foundation (by invitation)
b. On the future of graduate medical education, Ludwig Kast
c. Graduate medical education and the practitioner, John E. Jennings

Section Meetings

Section of Dermatology and Syphilis

Tuesday Evening, January 3, at 8:30 o'clock

ORDER

I. Presentation of Patients
a. Cases from Bellevue Hospital, Mihran B. Parounagian
b. Cases from Gouverneur Hospital, Josiah P. Thornley
c. Miscellaneous cases

II. Discussion

III. Executive Session
Note: Examination of cases is limited to members and their invited guests

Section of Surgery

Friday Evening, January 6, at 8:30 o'clock

ORDER

I. Reading of the Minutes

II. Presentation of Cases
a. Rectal intussusception complicating a malignant adenoma in intestinal polyposis, J. Gottesman

b. 1. A case of pneumo-peritoneum of unexplained origin
2. A case of diverticulosis of the large intestine, Russell H. Patterson

c. Carcinoma of the rectum—combined operation—immediate sacral vorlagerung, John C. A. Gerster

d. Two cases demonstrating the modified Miles operation for carcinoma of the lower sigmoid and rectum, Thomas H. Russell

e. Ball-valve colostomy, 2½ years after operation in case of adenocarcinoma of rectum, George A. Wyeth

III. Paper of the Evening
The operative treatment of cancer of the rectum, Daniel J. Jones, Boston (by invitation)

IV. Discussion opened by Drs. Dowd, Mathews, Pool and Yeomans

Section of Neurology and Psychiatry

The Section of Neurology and Psychiatry will hold a combined meeting with the Section of Obstetrics and Gynecology on Tuesday, January 24.

The program for the meeting will be announced in the second January folder.

Section of Pediatrics

(Hosack Hall)

Thursday Evening, January 12, at 8:30 o'clock

ORDER

I. Paper of the Evening
Endocrine glands in relation to infancy and childhood, Lewellys F. Barker, Baltimore (by invitation)

Discussion, George Draper, Charles R. Stockard, Frederick Tilney

Section of Otology

Friday Evening, January 13, at 8:30 o'clock

ORDER

I. Reading of the Minutes

II. Papers of the Evening

a. Anatomy of the lateral sinus and pathology of its infections, James Garfield Dwyer

b. Diagnosis and treatment of infections of the lateral sinus, George Loring Tobey, Jr., Boston (by invitation)

Discussion by William H. Haskin, John McCoy, John R. Page, T. Laurance Saunders

III. General Discussion

IV. Executive Session

Section of Ophthalmology

Monday Evening, January 16, at 8:30 o'clock

ORDER

I. Reading of the Minutes

II. Presentation of Cases
   a. Glioma of optic nerve, report of a case, Herbert W. Wootton
   b. Chorioretinae depigmentation accompanying generalized vitiligo, report of a case, David Wexler (by invitation)
   c. A case of trichinosis with exophthalmos, Ben Witt Key

III. Papers of the Evening
   a. A modified Motais operation for ptosis, Daniel B. Kirby
   b. Observations of the eye clinic of Dr. Henry T. Holland, at Shikarpur, India, with lantern slides and motion pictures, James Wilson Cassell
   c. Fundus as a definite index to arterial disease, with analysis of 100 cases, Sigmund A. Agatston

   Discussion by Harlow Brooks, Eli Moschcowitz, Ernst Boas

IV. Executive Session

Section of Medicine

Tuesday Evening, January 17, at 8:30 o'clock

Joint Meeting with the American Dietetic Association

ORDER

I. Paper of the Evening
   The control of protein in the diet, Eugene F. DuBois

II. Discussion
   Mary Swartz Rose (by invitation), Grace MacLeod (by invitation), Nellis B. Foster

Section of Genito-Urinary Surgery

Wednesday Evening, January 18, at 8:30 o'clock

ORDER

I. Reading of the Minutes

II. Presentation of Cases
   a. Cyst of the prostatic utricle, Samuel Lubash (by invitation)
   b. Supravesical hematuria due to renal infarction, Paul W. Aschner
   c. Bacillus coli infection of urinary system. X-ray studies, V. C. Pedersen

III. Papers of the Evening
   a. My personal experiences with tumors of the bladder, Arthur L. Chute, Boston (by invitation)
   b. A new procedure in the roentgen ray diagnosis of ureteral calculi, Ralph L. Dourmashkin

IV. General Discussion

V. Executive Session

Section of Orthopedic Surgery

Friday Evening, January 20, at 8:30 o'clock

ORDER

I. Reading of the Minutes

II. Papers of the Evening

a. Derotation, detorsion and stabilization of the fifth lumbar vertebra in scoliosis, Paul B. Steele, Pittsburgh (by invitation)

b. Some observations in an end result study, now being made of 348 cases of scoliosis treated at the New York Orthopedic Hospital by fusion, J. C. Risser (by invitation)

III. Discussion Opened by Russell A. Hibbs

IV. General Discussion

Section of Historical and Cultural Medicine

Friday Evening, January 20, at 8:30 o'clock

ORDER

I. Reading of the Minutes

II. Papers of the Evening

a. The life and work of George S. Huntington, Prof. Charles F. W. McClure, Princeton University (by invitation)
Discussion opened by Frederick Tilney, Samuel W. Lambert

b. The doctor looks at culture, Joseph Collins

Combined Meeting

Sections of Neurology and Psychiatry, and Obstetrics and Gynecology

Tuesday Evening, January 24, at 8:30 o'clock

ORDER

I. Reading of the Minutes

II. Clinical Presentations

a. Meralgia paraesthetica, James H. Huddleson

b. Meralgia paraesthetica—a new etiological conception and its treatment, Byron Stookey

Discussion, Frederick C. Freed, J. Ramsay Hunt

III. Papers of the Evening

a. The convulsive state—general considerations, Samuel Brock

b. The eclamptic convulsion, William E. Caldwell
Discussion, Nellis B. Foster, Harold C. Bailey, Edwin G. Zabriskie

c. Birth injuries from the neurological and obstetrical viewpoint, Richard N. Pierson, Leon H. Cornwall
Discussion, Bernard Sachs, Joseph R. Losee, Alfred S. Taylor, Benjamin P. Watson, Louis C. Schroeder

IV. Executive Session

SECTION OF LARYNGOLOGY AND RHINOLOGY

Monday Evening, January 23, at 8:30 o'clock

Note Change of Date

ORDER

I. PRESENTATION OF CASES
Neurosis of the nose, Wolff Freudenthal

II. PAPER OF THE EVENING
The diagnostic barium bougie and lesions at the lower end of the esophagus. Lantern slides, Harris P. Mosher, Boston (by invitation)

Discussion by Henry H. Forbes, Charles J. Imperatori

FEBRUARY

STATED MEETINGS

Thursday Evening, February 2, at 8:30 o'clock

I. EXECUTIVE SESSION

II. SYMPOSIUM: ALCOHOLISM

a. Alcohol—its public health aspects, its abuses and uses, Charles Norris, Chief Medical Examiner

b. A study of the alcoholic content of autopsy material, and its bearing on the cause of death, Alexander O. Gettler, Assistant Medical Examiner (by invitation)

Thursday Evening, February 16, at 8:30 o'clock

I. EXECUTIVE SESSION

II. PAPER OF THE EVENING
Animal reservoirs of human disease with special reference to microbic variability, Theobald Smith, Director, Department of Animal Pathology, Rockefeller Institute, Princeton

SECTION MEETINGS

SECTION OF SURGERY

Friday Evening, February 3, at 8:30 o'clock

ORDER

I. READING OF THE MINUTES

II. PRESENTATION OF CASES

a. 1. Recurrent volvulus of the sigmoid
2. Carbuncle of face, with staphylococcus sepsis and multiple bone foci
3. Bilateral fractures of the femur, followed by anuria. Recovery after decapsulation, A. Hyman

b. Cases illustrating the paper of the evening.

III. Papers of the Evening

a. The extension of the surgery of neoplastic diseases by endothermy, George A. Wyeth

b. Functional restoration as an element in facial repair. Lantern slides. Cinema demonstration, J. Eastman Sheehan

IV. Discussion

Section of Dermatology and Syphilis

Tuesday Evening, February 7, at 8:30 o'clock

ORDER

I. Presentation of Patients

a. Cases from the Polyclinic Hospital, Frederic Dillingham, Serafino Genovese, Jerome Kingsbury, Lawrence K. McCafferty, John Rothwell

b. Cases from the City Hospital, A. Benson Cannon

c. Miscellaneous cases

II. Discussion

III. Executive Session

Note: Examination of cases is limited to members and their invited guests.

Section of Pediatrics

Thursday Evening, February 9, at 8:30 o'clock

ORDER

I. The Ketogenic Diet in Epilepsy, Fritz Bradley Talbot, Boston (by invitation)

II. The Ketogenic Diet, M. G. Peterman, Milwaukee (by invitation)

III. Discussion, Kenneth M. Metcalf (by invitation), Israel Strauss, H. Rawle Geyelin (by invitation)

Section of Otology

Friday Evening, February 10, at 8:30 o'clock

ORDER

I. Reading of the Minutes

II. Clinical Meeting on Suppuration of the Petrous Pyramid

a. Report of case with pathological specimen, I. Friesner

b. Report of case, E. L. Pratt (by invitation)

c. Report of case, W. C. Bowers

d. Report of case with pathological specimen, R. T. Atkins

III. Discussion, Wells P. Eagleton, Foster Kennedy, Alfred S. Taylor, I. Friesner

IV. General Discussion

Section of Neurology and Psychiatry

Tuesday Evening, February 14, at 8:30 o'clock

ORDER

I. Reading of the Minutes

II. Symposium on Disorders of the Skin, Heart and Alimentary Canal Dependent Upon Disorders of the Central Nervous System

a. Some central connections of the vegetative nervous system, Smith Ely Jelliffe
b. Neurogenic and psychogenic disorders of the skin, Joseph J. Eller
c. Psychogenic disorders of the heart, John Wyckoff
d. Neurogenic disorders of the heart, Ernst P. Boas
e. Neurogenic and psychogenic disorders of the alimentary canal, John L. Kantor

Discussion, George M. MacKee, Fred Wise, Bernard S. Oppenheimer, Cary Eggleston, Walter A. Bastedo, Burrill B. Crohn, Foster Kennedy, Walter Timme, S. Philip Goodhart

III. Executive Session

Section of Genito-Urinary Surgery

Wednesday, February 15

Afternoon Program

to be presented at

The New York Hospital, 8 West 16th St.

1:30 P.M.—Administration of sacral and parasacral anesthesia, Roy B. Henline

1:45 P.M.—Perineal prostatectomy on above case, Oswald S. Lowsley

2:15 P.M.—Report cases suffering from right sided pain who have been operated upon without relief, Francis P. Twinem (by invitation)

2:20 P.M.—Report of a new antiseptic (rivanol dextrose) for local application to mucous surfaces of the urinary tract, T. Clement Hill (by invitation)

2:30 P.M. Demonstration of pictures by artist, William P. Didusch (by invitation)

2:45 P.M.—Administration of paravertebral anesthesia, Roy B. Henline

3:00 P.M.—Nephrectomy on above case, Oswald S. Lowsley

3:30 P.M.—Demonstration of cases of incontinence of urine operated upon, Raymond M. Bowles (by invitation)

3:45 P.M.—Report on cases of polycystic kidney, Lisle B. Kingery (by invitation)

4:00 P.M.—Administration of sacral and parasacral anesthesia, Roy B. Henline

4:15 P.M.—Perineal prostatectomy on above case, Oswald S. Lowsley

4:40 P.M.—Demonstration of interesting pyelograms and post-operative cases, V. A. Nardiello (by invitation), Peter Lavalle (by invitation), F. C. Steinmetz (by invitation), J. R. Whisenant, R. Zeiss (by invitation), John Toole (by invitation), Cyril K. Church (by invitation), John Duff (by invitation), J. K. DeVries (by invitation), P. L. Helmick (by invitation).

5:00 P.M.—Ward rounds, Oswald S. Lowsley and staff

EVENING PROGRAM

to be presented at

THE NEW YORK ACADEMY OF MEDICINE

8:30 o'clock

a. Comparative anesthetic activity of various local anesthetics including novocaine borate and tutocaine for the mucous surfaces of the urinary tract (5 min.), George A. Fiedler (by invitation)
b. Case of spontaneous rupture of kidney due to malignant papilloma of the kidney pelvis (5 min.), Hubert A. Lyons (by invitation)
c. The treatment of inoperable and post-operative cases of tuberculosis of the urinary tract (10 min.), William R. Delzell (by invitation), Stanley Wang (by invitation)
d. Report of case showing tbc. in urine but no lesions in kidney (10 min.), Robert Gutierrez (by invitation)
e. Pathological report of unusual specimens removed at operation (10 min.), Gilbert Daldorf (by invitation)
f. Operative methods employed in kidney surgery (lantern slide demonstration) (10 min.), Thomas J. Kirwin
g. Urological conditions in women (lantern slide demonstration) (10 min.), Frederick T. Lau
h. Certain urological problems in children with report of cases (lantern slide demonstration) (10 min.), Paul M. Butterfield
i. Operations upon the prostate gland (30 min.), Oswald S. Lowsley

SECTION OF ORTHOPEDIC SURGERY

Friday Evening, February 17, at 8:30 o'clock

ORDER

I. READING OF THE MINUTES

II. CASE PRESENTATIONS ILLUSTRATING OPERATIONS FOR OLD CONGENITAL DISLOCATION OF THE HIP

a. Shelf operation, 3 cases, Armitage Whitman
b. Deepening of acetabulum, 1 case, Irving Balensweig
c. Bifurcation operation, 1 case, Walter I. Galland (by invitation)

III. Papers of the Evening

a. Operative treatment of old congenital dislocation of the hip. Lantern slides, A. Bruce Gill, Philadelphia (by invitation)

b. A review of end results of the treatment of congenital dislocation of hip, Richmond Stephens

Section of Ophthalmology

Monday Evening, February 20, at 8:30 o'clock

ORDER

I. Reading of the Minutes

II. Presentation of Cases

a. 1. Synchisis scintillans of the anterior chamber
2. Thirty year old lachrymal gland tumor
3. Bi-lateral irido-cyclitis (tubercular) precipitated by mild trauma, Ralph I. Lloyd

b. 1. Halo in glaucoma as seen and drawn by patient
2. Cataract extraction ten years ago, in a case of retinitis pigmentosa, L. W. Crigler

c. Gumma of orbit, Kaufman Schlivek

d. A button-like epithelioma involving the entire upper eye lid, cured by supersoft Roentgen rays, Joseph Jordan Eller

III. Paper of the Evening

Eye and orbit phase of cancer work at the New York Skin & Cancer Hospital, George H. Semken

IV. Executive Session

Section of Medicine

Tuesday Evening, February 21, at 8:30 o'clock

ORDER

I. Papers of the Evening

a. Dosage and clinical use of intravenous digitalis therapy, Harold E. B. Pardee

b. The cardio-tachometer: an instrument to count the totality of heart beats over a long period of time, Ernst P. Boas

II. Discussion by T. Stuart Hart, Frank J. McGowan, Jr.

Section of Laryngology and Rhinology

Thursday Evening, February 23, at 8:30 o'clock

Note Change in Date

I. Reading of the Minutes

II. Presentation of Cases and Short Papers

a. 1. Rhinolith necessitating external nasal operation for its removal
2. Foreign body,—large piece of gauze in nose diagnosed as carcinoma, unexpectedly removed
3. Improved local anesthesia for antrum puncture, M. C. Myerson

b. 1. Teratoma of the naso-pharynx,—operation and end result
2. Lympho-sarcoma of the tonsil,—operation and end result, John M. Loré

c. Radium in rhinoscleroma, G. Allen Robinson

d. Surgical diathermy made possible in tonsil enucleation, F. Peter Herman (by invitation)

e. Unusual pathological findings in the nose and throat. Lantern slide demonstration, Louise H. Meeker (by invitation)

SECTION OF OBSTETRICS AND GYNECOLOGY

Tuesday Evening, February 28, at 8:30 o'clock

ORDER

I. READING OF THE MINUTES

II. PRESENTION OF CASE

A case of spontaneous rupture of a pyosalpinx into the urinary bladder, S. di Palma, Meyer M. Stark.

Discussion opend by Walter T. Dannreuther

III. PRESENTION OF INSTRUMENT

A self-retaining vaginal retractor, Isador W. Kahn.

IV. PAPERS OF THE EVENING

a. A simplified method of testing tubal patency, I. Seth Hirsch, N. Shnayerson (by invitation)

b. The treatment of asphyxia neonatorum by means of alpha-lobelin injected into the umbilical vein, Robert A. Wilson (by invitation)

Discussion opened by Eliot Bishop (by invitation)

V. GENERAL DISCUSSION

VI. EXECUTIVE SESSION

RECENT ACCESSIONS TO THE LIBRARY

Adler, A. Understanding human nature.
N. Y., Greenberg, 1927. 286 p.

Aikens, C. A. Primary studies for nurses. 6. ed.
Phila., Saunders, 1927. 572 p.

American men of science. Ed. by J. M. Cattell & J. Cattell. 4. ed.
N. Y., Science press, 1927. 1132 p.

Barduzzi, D. Manuale di storia della medicina. [18.-19. century.]
Sten., Soc. tipo.-ed. naz., 1927. 299 p.

Bassler, A. Diseases of the intestines, 3. ed.
Phila., Davis, 1928. 905 p.

Bedside diagnosis by American authors, ed. by G. Blumer.
Phila., Saunders, 1928. 3 vols.

Birnbaum, K. Die psychopathischen Verbrecher. 2. Aufl.
Leip., Thieme, 1926. 287 p.

Collins, J. A doctor looks at doctors.
N. Y., Harper, 1927. 32 p.

Contributions to medical science: dedicated to Alfred Scott Warthin.
Ann Arbor, Wahr, 1927. 720 p.

Cumberbatch, E. P. Diathermy. 2. ed.
Lond., Heinemann, 1927. 332 p.

Delmas-Marsalet, P. Les réflexes de posture élémentaires.
Paris, Masson, 1927. 174 p.

Derennes, C. Amours et crimes.
Paris, Ed. de France, 1927. 306 p.

Dietrich, A. Grundriss der allgemeinen Pathologie.
Leip., Hirzel, 1927. 324 p.

Dudgeon, L. S. Bacterial vaccines.
Lond., Constable, 1927. 87 p.

Dudley, E. C. The medicine man: being the memoirs of fifty years of medical progress.
N. Y., Sears, 1927. 369 p.

Duesberg, J. L'oeuf et ses localisations germinales.
Paris, Pres. univ. de France, 1926. 107 p.

Ehlers, V. M. and Steel, E. W. Municipal and rural sanitation.
N. Y., McGraw-Hill, 1927. 448 p.

Endleman, J. Special dental pathology. 2. ed.
Lond., Kimpton, 1927. 444 p.

Fendel, H. Die vegetative Neurose als kausaler Faktor in der Genese körperlicher und seelischer Erkrankungen.
Frankfurt a.M., Werner, 1927. 108 p.

Fischer, A. Gewebezüchtung. 2. Ausg.
München, Müller, 1927. 508 p.

Foster, Wm. The romance of chemistry.
Lond., Allen, 1927. 468 p.

Fuchs, J. Technische Operationen in der Orthopädie.
Berlin, Springer, 1927. 230 p.

Gallichan, W. M. The psychology of marriage.
Lond., Laurie, 1927. 248 p.

Gordon, R. G. The neurotic personality.
Lond., Kegan Paul, 1927. 300 p.

Great Britain. Report of the Departmental committee on the treatment of young offenders.
Lond., H. M. S. off., 1927. 139 p.

Guttmann, G. Haut-und Infektions-Krankheiten.
Berlin, Meusser, 1926. 163 p.

Gwynne-Vaughan, H. C. L. and Barnes, B. The structure and development of the fungi.
Cambridge, Univ. pr., 1927. 384 p.
Hahn, B. Die Morphin-Erkrankungen.
Heidelberg, H. Grossberger, 1927. 165 p.
Hanslian, R. Der chemische Krieg. 2. Aufl.
Berlin, Mittler, 1927. 411 p.
Henry, A. K. Exposures of long bones and other surgical methods.
Bristol, Wright, 1927. 80 p.
Hill, A. V. Muscular movement in man.
N. Y., McGraw-Hill, 1927. 104 p.
Hitzenberger, K. Das Zwerchfell.
Wien, Springer, 1927. 206 p.
Hoffmann, H. Das Problem des Charakteraufbaus.
Berlin, Springer, 1926. 193 p.
Holmes, S. J. The biology of the frog. 4. ed.
N. Y., Macmillan, 1927. 386 p.
Hoxie, G. H. Medicine for nurses. 2. ed.
Phila., Saunders, 1928. 449 p.
Huntington, E. The human habitat.
N. Y., Van Nostrand co., 1927. 293 p.
International (First) orthodontic congress. 1926. [Transactions, etc.]
St. Louis, Mosby, 1927. 767 p.
Jeans, T. T. Reminiscences of a naval surgeon.
Lond., Sampson Low, 1927. 310 p.
Jordan, H. J. Uebungen aus der vergleichenden Physiologie.
Berlin, Springer, 1927. 272 p.
Keith, Sir A. Concerning man's origin.
Lond., Watts, 1927. 54 p.
Kofler, L. Die Saponine.
Wien, Springer, 1927. 278 p.
Korbsch, R. Lehrbuch und Atlas der Laparo-und Thorakoskopie.
München, Lehmann, 1927. 73 p.
Kraus, R. 10 Jahre Südamerika. Vorträge über Epidemiologie und Infektionskrankheiten.
Jena, Fischer, 1927. 182 p.
Lehmann, A. Aberglaube und Zauberei von den ältesten Zeiten an bis in die Gegenwart. 3. Aufl.
Stuttgart, Enke, 1925. 752 p.
Leroy, E. B. Les visions du demi-sommeil.
Paris, Alcan, 1926. 131 p.
Liber, B. The child and the home.
N. Y., Vanguard pr., 1927. 248 p.
Low, R. C. The common diseases of the skin.
Edinb., Oliver, 1927. 223 p.
Macgregor, M. E. Mosquito surveys.
Lond., Baillière, 1927. 293 p.
McKenzie, D. Diseases of the throat, nose and ear. 2. ed.
Lond., Heinemann, 1927. 677 p.
Martin, E. G. and Weymouth, F. W. Elements of physiology.
Phila., Lea, 1928. 784 p.
Matuschka, J. and Rosner, R. Die Malariatherapie der Syphilis.
Wien, Springer, 1927. 84 p.
Mead, S. V. Diseases of the mouth.
St. Louis, Mosby, 1927. 578 p.
Moon, R. O. Growth of our knowledge of heart disease.
Lond., Longmans, 1927. 86 p.

Morgan, T. H. Experimental embryology.
N. Y., Col. univ. pr., 1927. 766 p.
Nelson loose-leaf living surgery. Editor in chief A. D. Whipple. 4 vols.
N. Y., Nelson, 1927.
Nowak, J. Documenta microbiologica. [Atlas]. Th. I. Bakterien.
Jena, Ficsher, 1927. 162 p.
Panton, P. N. and Marrack, J. R. Clinical pathology. 2. ed.
Lond., Churchill, 1927. 459 p.
Piéron, H. Thought and the brain.
Lond., Kegan Paul, 1927. 262 p.
Pauchet, V. [et al.]. L'anesthésie régionale. 4. éd.
Paris, Doin, 1927. 382 p.
Peltason, F. Grundzüge der Röntgendiagnostik innerer Erkrankungen.
München, Bergmann, 1927. 178 p.
Pende, N. Trattato sintetico di patologia e clinica medica. v.1.
Messina, M. Principato, 1927.
Petty, Sir Wm. The Petty papers. Some unpublished writings.
Lond., Constable, 1927. 276 p.
Piéron, H. Thought and the brain.
Lond., Kegan Paul, 1927. 262 p.
Pitt-Rivers, G. H. L. The clash of culture and the contact of races.
Lond., Routledge, 1927. 312 p.
Porot, A. Les syndromes mentaux. v.1.
Paris, Doin. 1928.
Putti, V., and Camucati, M. I tumori delle ossa e la loro cura.
Bologna, 1927. 159 p.
Rosenfeld, G. Diätkuren.
Berlin, Fischer, 1927. 176 p.
Roskam, J. Physiologie normale et pathologique du globulin.
Paris, Pr. univ. d. France, 1927. 151 p.
Rost, H. Bibliographie des Selbstmords.
Augsburg, Haas, 1927. 391 p.
Royster, H. A. Appendicitis.
N. Y., Appleton, 1927. 370 p.
St. Hill, K. Medical palmistry.
Lond., Rider, [1927]. 132 p.
Schlegel, E. Die Krebskrankheit.
Stuttgart, Hippok, verl., 1927. 291 p.
Seifried, O. Die wichtigsten Krankheiten des Kaninchens.
München, Bergmann, 1927. 100 p.
Seligmann, E. Seuchenbekämpfung.
Berlin, Karger, 1928. 282 p.
Shennan, T. Post mortems and morbid anatomy. 2. ed.
Lond., Sci. pr., 1927. 664 p.
Short, A. R., and Ham, C. I. A synopsis of physiology.
Bristol, Wright, 1927. 258 p.
Sobotta, J. Atlas of human anatomy. 3 vols.
N. Y., Stechert, 1927-28.
Statesman and friend. Correspondence of John Adams, with Benjamin Waterhouse. 1784-1822. Edited by W. C. Ford.
Bost., Little, 1927. 178 p.
Stiles, P. G. Dreams.
Cambridge, Harvard univ. pr., 1927. 80 p.
Taylor, F. L. Crawford W. Long and the discovery of ether anesthesia.
N. Y., Hoeber, 1927. 237 p.
Thiel, P. J. Praktische Iriswissenschaft.
Leip., Krüger, 1927. 64 p.

Tómasson, H. Undersogelser over nogle af blodets elektrolytes (CA, K, NA, H), og det vegetative nervesystem.
Kobenhavn, Levin, 1927. 257 p.
Transactioons of the American neurological association for 1926.
Waldschmidt-Leitz, E. Die Enzyme.
Braunschweig, Vieweg, 1926. 233 p.
Weidenreich, F. Rasse und Körperbau.
Berlin, Springer, 1927. 187 p.
Whipple, G. C. The microscopy of drinking water. 4. ed.
N. Y., Wiley, 1927. 585 p.
Whitehead, A. N. Symbolism.
N. Y., Macmillan, 1927. 88 p.

FELLOWS ELECTED FEBRUARY 2

Mortimer N. Hyams, M.D., 78 East 79th Street.
Philip Raphael Lehrman, M.D., 120 Riverside Drive.
Samuel P. Oast, M.D., 30 East 40th Street.
Henry B. Orton, M.D., 24 Commerce Street, Newark, N. J.
Algernon Beverly Reese, M.D., 50 West 52nd Street.
Samuel Rosen, M.D., 36 East 73rd Street.
Irving Schwartz, M.D., 1150 Fifth Avenue.
Carolyn Gay Williamson, M.D., 545 West 146th Street.

DEATHS OF FELLOWS

GEORGE REESE SATTERLEE, A.B., A.M., M.D., 9 East 40th Street, New York City, graduated in medicine from the College of Physicians and Surgeons, New York City, in 1898; elected a Fellow of the Academy, January 5, 1905; died February 8, 1928. Dr. Satterlee was a Fellow of the American Medical Association, a member of the American Therapeutic Society, the American Gastro-Enterological Society, the Gastro-Enterological Society, the Pathological Society, and Attending Physician at Fordham Hospital. He was also Consulting Physician to the New Jersey State Hospital.